



PDFFREE COMUNIDAD ODONTOLOGICA

Oral and Maxillofacial Medicine

CRISPIAN SCULLY CBE



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Oral and Maxillofacial Medicine

THE BASIS OF DIAGNOSIS AND TREATMENT

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Edinburgh London New York Oxford Philadelphia St Louis Sydney Toronto 2004

WRIGHT

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First published 2004

Reprinted 2004

ISBN 0723 61074 6

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

Library of Congress Cataloging in Publication Data

A catalog record for this book is available from the Library of Congress

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Printed in China

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Preface

Oral medicine is that area of special competence in dentistry concerned mainly with diseases involving the oral and perioral structures, especially the oral mucosa, and the oral manifestations of systemic diseases. The specialty, in some countries termed 'stomatology', deals not only with oral disease but also with perioral lesions, and is increasingly known as 'oral and maxillofacial medicine'. Furthermore, apart from the obvious close relationships with oral pathology (oral and maxillofacial pathology) and with oral surgery (oral and maxillofacial surgery), there is a close relationship with special care dentistry and hospital dentistry.

This book attempts to present for those interested in oral medicine and hospital dentistry, the basics of the specialty of oral medicine in a useful and digestible format; by offering the information in a range of modes and levels of detail and offering practical guidance to diagnosis, therapy and sources of information for patient and clinician, both on the Internet and elsewhere.

The first section reviews the fundamental principles of the history, examination and investigations and principles of management. In the absence of randomised controlled trials, many of the therapies suggested are unable to be thoroughly evidence-based. Hopefully, future multicentre studies will rectify this deficiency. The second section discusses the more common symptoms and signs in oral medicine.

The third section covers in some detail the most common and important conditions seen in oral medicine. This section also includes synopses of a number of eponymous and other conditions relevant to oral medicine; if a specific condition is not found there, the reader is referred to the index, since it may well be located elsewhere in the book.

The fourth section is a discussion of the important areas of HIV infection and iatrogenic diseases.

The other relevant oral manifestations of systemic disorders are tabulated in Appendix 1: further detail can be found in *Medical Problems in Dentistry* (Scully and Cawson: Elsevier, Edinburgh, 2004).

Agents used in the treatment of patients with oral diseases are outlined in Appendix 2. Only a limited number of these are prescribed by dental practitioners, but practitioners may have to cope with questions from patients

about their treatment, or to recognise or deal with treatment complications. Further details can be found in textbooks such as *Basic Pharmacology And Clinical Drug Use In Dentistry* (Cawson, Spector and Skelly: Churchill Livingstone, Edinburgh, 1995).

An attempt has been made to present the material in such a way as to highlight the more important conditions – important because of frequency or seriousness – and to guide the reader through didactic and problem-oriented approaches. However, it is impossible to position every subject in a perfect location, not least because few conditions affect only one site (e.g. even erythema migrans can have lesions in sites other than on the tongue), some affect even more than one tissue (e.g. ectodermal dysplasia affects skin, salivary glands and teeth) and several have a range of clinical presentations (e.g. lichen planus and cancer can both present with white, red or ulcerative lesions, and can be symptomless or cause extreme discomfort). Cross-refering between sections will help the user get full value from the content.

The book is not intended to give all the details of the various investigative and therapeutic modalities, since these are covered in other texts by the author, or in pharmacopoeias. The book offers illustrative examples of the more common and important conditions, but cannot provide the more comprehensive selection of illustrations such as can be found in atlases such as *Oral Diseases* (Scully, Flint, Porter and Moos: Dunitz, London, 2004).

I thank my patients and nurses who have taught me so much over the years, and continue so to do, and all those students and colleagues with whom I have worked and interacted, who may have shared the clinical care of some patients, and/or may have knowingly or otherwise contributed ideas or content.

In this respect I thank especially Professors Oslei Almeida (Brazil), Jose-Vicente Sebastian-Bagan (Spain), Johann Beck-Managetta (Austria), Roman Carlos (Guatemala), Marco Carrozzo (Italy), Roderick Cawson (UK), Pedro Diz Dios (Spain), Dore Eisen (USA), Joel Epstein (Canada), Sergio Gandolfo (Italy), George Laskaris (Greece), Jens Pindborg (Denmark; deceased), Stephen Porter (UK), Peter Reichart (Germany), Pierre-Luigi Sapelli (Italy), Sol 'Bud' Silverman (USA) and Isaac Van der Waal (The Netherlands).

Thanks are also due to: Alan Drinnan (USA) for his innovative introduction of the Bulletin Board in Oral Pathology (BBOP), a useful world forum for oral medicine and pathology; to Miguel Lucas-Tomas (Spain), who founded the European Association for Oral Medicine – a major European forum; and to Dean Millard (USA) and David Mason (UK), who had the foresight to institute the World Workshops in Oral Medicine; to John Greenspan (USA) who had the foresight to organise the Oral AIDS workshops; and to Newell Johnson with whom I founded and co-edit *Oral Diseases*. These giants have helped the progression of oral medicine to the high level at which it now stands.

Much of my work could not be done without the support of my family (Zoe and Frances) and my work colleagues who help with information collection, particularly John Evans, Avril Gardner, Lesley Garlick and Karen Widdowson, to whom thanks are due. I thank Jose-Vicente Sebastian Bagan and Isaac van der Waal, and also my nephew, Dr Athanassios Kalantsis, for their helpful, friendly and constructive comments on the text.

Finally, I would be delighted to receive any comments about this text, in the hope that I can improve further in the future.

CS

London 2003

SECTION I

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Fundamental Principles of Patient Management

1

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Diagnosis: History

It is better to know what kind of patient has the disease than what kind of disease the patient has.

Sir William Osler

Introduction

Diagnosis means 'through knowledge' and entails acquisition of data about the patient and their complaint using the senses:

- hearing
- observing
- touching
- sometimes smelling.

The purpose of making a diagnosis is to be able to offer the most:

- effective and safe treatment
- accurate prognostication.

Diagnosis is made by the clinical examination, which comprises the:

- history
- physical examination
- supplemented in some cases by investigations.

Each is based on a thorough, methodical routine. Diagnosis most importantly involves a careful history; the patient will often deliver the diagnosis from the history, though the findings from examination and investigations can be helpful. To state the obvious, it is difficult to diagnose a condition that is unknown to the diagnostician; thus extensive reading of

recent literature, clinical experience and discussion with colleagues is continually needed, as well as an enquiring mind. Continuing education is essential.

There are many types of diagnosis, including:

- Clinical diagnosis: made from the history and examination.
- Pathological diagnosis: provided from the pathology results.
- Direct diagnosis: made by observing pathognomonic features. This is occasionally possible, for example in dentinogenesis imperfecta where the abnormally translucent brownish teeth are characteristic.
- Provisional (working) diagnosis: the more usually made diagnosis. This is an initial diagnosis from which further investigations can be planned.
- Deductive diagnosis: made after due consideration of all facts from the history, examination and investigations.
- Differential diagnosis: the process of making a diagnosis by considering the similarities and differences between similar conditions.
- Diagnosis by exclusion: identification of a disease by excluding all other possible causes.
- Diagnosis ex-juvantibus: made on the results of response to treatment. For example, the pain of trigeminal neuralgia may be atypical, and the diagnosis can sometimes be confirmed only by a positive response to the drug carbamazepine.
- Provocative diagnosis: the induction of a condition in order to establish a diagnosis. This is rarely needed, except in possible drug reactions or allergies, when the patient may need to be re-exposed to the potentially culpable substance, but this should always be carried out where appropriate medical support and resuscitation are available.

History taking

The first contact with the patient is crucial to success and there should be a courteous approach to the patient with a professional introduction and every effort to establish communication, rapport and trust and make the patient feel the focus of the clinician's interest. History taking is part of the initial communication between the dentist and patient. It is important to adopt a professional appearance and manner, and introduce oneself clearly and courteously. The patient will know if you care, well before they care if you know.

The clinician should encourage the patient to tell the story in their own words, and use methodical questioning to elucidate further details.

Perhaps not surprisingly, many patients are apprehensive when confronted by a clinician, and therefore they may be easily disturbed if, for

example, the clinician appears indifferent or unsympathetic. This can result in barriers to effective communication which will simply hinder the clinician.

Due cognisance must also always be taken of the age, cultural background, understanding and intelligence of the patient when taking the history. It is the clinician's responsibility to elicit an accurate history; if that necessitates finding an interpreter, for example, then the clinician must arrange this.

The history is best given in the patient's own words, though the clinician often needs to guide the patient, and may use protocols to ensure collection of all relevant points.

It is important to cover the following areas:

- general information (name, age, gender, ethnic origin, place of residence, occupation)
- presenting complaint
- history of the present complaint
- past medical history
- dental history
- family history
- social history.

By the end of the history, the clinician should have an idea of the patient's concerns, have assessed the patient's current problems and also have drawn up a provisional or differential diagnosis.

Presenting complaint

The history taking commences by identifying the current complaint(s), e.g. 'sore mouth'. The 'history of the present complaint' is then taken.

History of the present complaint

This should cover aspects relevant to the particular main complaint, such as:

- date of onset
- duration
- location(s)
- aggravating and relieving factors
- investigations thus far
- treatment already received.

'Leading questions' (i.e. those which suggest the answer) should be avoided. 'Open questions', which do not suggest an answer, are preferred. The history should be directed by the complaint. Then a series of relevant questions should elicit the 'past or relevant medical history'.

Past or relevant medical history

PDFFREE.COM The medical history should be taken to elicit all matters relevant to the:

- diagnosis
- treatment
- prognosis.

As a double check on the verbal history, the use of preprinted, standardised, self-administered questionnaires is helpful, and may encourage more truthful responses to sensitive questions.

The history should uncover, for example, medical history relevant to:

- Previous episodes of similar or related complaints.
- Other complaints that may be relevant. For example, in patients with mucosal disorders, it is important to ascertain whether there have been lesions affecting other mucosae (ocular or anogenital) or skin.

Important to include are:

- General symptoms, such as fever or weight loss.
- Relevant symptoms related to body systems, such as:
 - nervous system (e.g. sensory loss)
 - gastrointestinal disorders that may be associated with oral ulcers and other lesions
 - skin lesions (solitary or rashes), itch or discolourations which are common symptoms of skin disease and there are sometimes oral lesions
 - ocular problems
 - anogenital lesions
 - psychiatric disorders, such as anxiety and depression, and drug abuse are relevant to orofacial pain and other symptoms.
- Medical or surgical consultations, investigations and treatments, including radiotherapy.
- Current prescribed drugs (including alternative medicines), since these may cause oral complaints or influence management.
- Self-medications.
- Complementary medicine.
- Allergies.
- Previous illnesses.
- Hospitalisations.
- Operations.
- Anaesthetics.
- Specific medical problems that may influence operative procedures, particularly:
 - bleeding tendency
 - corticosteroid therapy

diabetes

cardiac problems

endocarditis risk.

Patients may also carry formal warnings of certain conditions relevant to dental care. These may be written cards, smart cards, bracelets or necklaces.

The medical history of dental patients should be directed to elicit any relevant systemic disease. For example:

- **Anaemia:** a reduction in haemoglobin level below the normal for age and sex. It can:
 - be a contraindication to general anaesthesia
 - cause oral complications (i.e. sore mouth, burning tongue, glossitis, ulcers, angular stomatitis).
- **Bleeding tendency:** a hazard to any surgical procedure, including some injections, and a contraindication to aspirin and some other non-steroidal anti-inflammatory drugs (NSAIDs).
- **Cardiorespiratory disease:** this may be a contraindication to general anaesthesia. Cardiac patients may need antimicrobial cover to prevent infective endocarditis or may have a bleeding tendency because of anti-coagulants. Patients with various cardiac lesions are predisposed to develop endocarditis, which may be precipitated as a consequence of the bacteraemia associated with some forms of dental treatment.
- **Drug use, allergies and abuse:** these may give an indication about underlying pathology, or may influence dental procedures or drug use. Drug allergies are a contraindication to the use of the responsible or related drugs. Drug abuse may give rise to behavioural problems and a risk of cross-infection. Corticosteroids absorbed systemically produce adrenocortical suppression. Such patients cannot respond adequately to the stress of trauma, operation or infection, and stress may produce adrenal crisis and collapse.
- **Endocrine disease.** Diabetes may cause:
 - the danger of hypoglycaemia if meals are interfered with
 - oral complications such as sialosis, dry mouth and periodontal breakdown.
 Hyperparathyroidism may cause:
 - jaw radiolucencies/rarefaction
 - loss of lamina dura
 - giant cell granulomas (central)
 - hypercalcaemia.
- **Fits and faints:** epilepsy and other causes of unconsciousness should be elicited before embarking on any procedures.
- **Gastrointestinal disorders:** are relevant mainly because of possible vomiting with general anaesthesia, and possible oral manifestations.

- Hospital admissions, attendances and operations: this information often helps fill in gaps in the medical history, and may be relevant if, for example, the patient has had a previous halothane anaesthetic or has had radiotherapy. Surgery in the absence of any serious postoperative haemorrhage also suggests the absence of any inherited bleeding tendency.
- Infections: the possibility of transmission of infection to patients or staff is ever present:
 - blood-borne infections – hepatitis viruses B and C, and HIV are the main agents of concern
 - respiratory infections – current or very recent respiratory infections, particularly tuberculosis, may be a contraindication to general anaesthesia
 - sexually transmitted diseases – imprecise diagnosis or empirical treatment serves only to spread these infections, as contact tracing is normally undertaken only on proven cases of sexually transmitted (venereal) disease.
- Jaundice and liver disease: these are important because of their influence on bleeding tendency, drug intolerance and possible viral hepatitis.
- Kidney disease: this may cause a bleeding tendency and impaired drug excretion. The other main problems are in relation to the immunosuppression created following a kidney transplant.
- Likelihood of pregnancy: because of the danger of abortion or teratogenicity, it is important during pregnancy, particularly the first trimester, to avoid or minimise exposure to drugs, radiography and infections. Pregnancy can influence some conditions such as aphthae and Behçet syndrome, and may produce gingivitis or epulides.
- Malignant disease, including those on radiotherapy or chemotherapy: malignant disease may underlie some oral complaints such as pain or sensory changes and can result in significant morbidity and even mortality.
- Prosthesis and transplant patients: patients after transplants may be at risk from infection, neoplasms and iatrogenic problems, such as a bleeding tendency, gingival hyperplasia or graft-versus-host disease. Patients with transplants are also liable to present a number of complications to dental treatment – in particular the need for a corticosteroid cover, a liability to infection and a bleeding tendency. There is no good evidence for infection of prosthetic joints arising from oral sepsis. However, if the orthopaedic surgeon wishes an antimicrobial cover, the dentist must consider the medicolegal implications.

The complications of infection of ventriculo-atrial valves are so serious that, although as in the case of prosthetic joints there is little evidence for an oral source, it may be reasonable to give an antimicrobial cover, if the responsible neurosurgeon so advises. Patients

with pacemakers may be in danger in relation to the use of equipment which may interfere with their pacemaker, such as diathermy and electrosurgery.

- **Other relevant conditions:** every condition which is elicited from the medical history should be checked for relevance, but the following can be highly relevant:
 - malignant hyperthermia (malignant hyperpyrexia) – various general anaesthetics and other agents may be contraindicated
 - porphyria – intravenous barbiturates, metronidazole and other agents may be contraindicated
 - suxamethonium sensitivity – suxamethonium is contraindicated
 - hereditary angioedema – any dental trauma may result in oedema and a hazard to the airway
 - rheumatoid arthritis – cervical spine involvement may predispose to spinal cord damage if the neck is flexed during general anaesthesia.
 - Sjögren syndrome is a common complication
 - glucose-6-phosphate dehydrogenase deficiency is a contraindication to some drugs.

Dental history

The dental history will give an idea of the:

- regularity of attendance for dental care
- attitude to dental treatment
- recent relevant dental problems
- recent restorative treatment.

Family history

This may reveal hereditary problems, such as haemophilia, and familial conditions, such as diabetes.

Social history

The social history may reveal:

- whether the patient has family or a partner and the degree of support that can be anticipated
- information about the patient's residence, which can suggest the socio-economic circumstances of the patient
- information about contacts with pets and other animals, which may be relevant to some infectious diseases, such as cat-scratch disease or toxoplasmosis
- whether the patient has travelled overseas, which may be relevant to some infectious diseases, such as tropical diseases and deep mycoses

System	Specific problems	No	Yes
CVS	Heart disease, hypertension, angina, syncope		
	Cardiac surgery, rheumatic fever, chorea		
	Bleeding disorder, anticoagulants, anaemia		
RS	Asthma, bronchitis, TB, other chest disease, smoker		
GU	Renal, urinary tract or sexually transmitted disease		
	Pregnancy, menstrual problems		
GI/liver	Coeliac disease, Crohn's disease		
	Hepatitis, other liver disease, jaundice		
CNS	CVA, multiple sclerosis, other neurological disease		
	Psychiatric problems, drug or alcohol abuse		
	Sight or hearing problems		
LMS	Bone, muscle or joint disease		
Endocrine	Diabetes, thyroid, other endocrine disease		
Allergy	Allergies: e.g. penicillin, aspirin, plaster		
Drugs	Recent or current drugs/medical treatment		
	Corticosteroids, anticoagulants		
Others	Previous operations, general anaesthesia (GA) or serious illness		
	Other conditions (including congenital abnormalities)		
	Family medical history		
	Born, residence or travel abroad		
	Pets		
System CVS cardiovascular system RS respiratory system GU genitourinary GI gastrointestinal CNS central nervous system LMS locomotor system			

Figure 1.1 Systematic recording of relevant medical history

- the patient's sexual history, which may be relevant to some infectious diseases, such as HIV disease and hepatitis
- any occupational problems, which may be relevant to some disease, and access to care
- relevant habits (smoking, alcohol consumption and recreational drugs use) – tobacco use underlies several oral diseases, including periodontal disease and cancer
- information about the patient's diet – dietary fads may lead, for example, to vitamin deficiencies and glossitis or angular cheilitis.

Standardised forms will help with the recording of data, the relevance of which can sometimes be surprising (Fig. 1.1).

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2

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Diagnosis: Examination

The patient will know if you care, well before they care if you know.

Anonymous

Introduction

The clinical examination of the patient should start as the patient enters the clinic and is greeted by the clinician. The history and clinical examination are designed to put the clinician in a position to make a provisional diagnosis, or a differential diagnosis. Special tests or investigations may be required to confirm or refine this diagnosis or elicit other conditions. Physical disabilities, such as those affecting gait, and learning disability are often immediately evident as the patient is first seen, and blindness, deafness or speech and language disorders may be obvious. You should also be able to assess the patient's mood and general well-being, but if in any doubt ask for advice. Other disorders, such as mental problems, may become apparent at any stage. As a general rule, if you think a patient looks ill, they probably are. The patient should be carefully listened to during history taking and examination; speech and language can offer a great deal of information about the medical and mental state.

A patient has the right under common law to give or withhold consent to medical examination or treatment. This is one of the basic principles of healthcare. Patients are entitled to receive sufficient information in a way they can understand about the proposed treatments, the possible alternatives and any substantial risk or risks which may be special in kind or

magnitude or special to the patient, so that they can make a balanced judgment (UK Health Department, 19.2.99. HSC 1999/031),

Always remember that the patient has the right to refuse all or part of the examination. There may be cultural sensitivities but, in any case, no examination should be carried out in the absence of a chaperone – preferably of the opposite sex to the practitioner.

General examination

Medical problems may manifest in the fully clothed patient with abnormal appearance or behaviour, conscious level, movements, breathing, facial colour or wasting. General examination may sometimes include the recording of body weight and the 'vital signs' of conscious state, temperature, pulse, blood pressure and respiration. The dentist must be prepared to interpret the more common and significant changes.

Vital signs

- The conscious state.
- The temperature: the temperature is traditionally taken with a thermometer, but temperature-sensitive strips and sensors are available. Leave the thermometer in place for at least 3 minutes. The normal body temperatures are: oral, 36.6°C; rectal, 37.4°C; and axillary, 36.5°C. Body temperature is usually slightly higher in the evenings.
- The pulse: this can be measured manually or automatically. The pulse can be recorded from any artery, but in particular from the following sites:
 - the radial artery, on the thumb side of the flexor surface of the wrist
 - the carotid artery, just anterior to the mid-third of the sternomastoid muscle
 - the superficial temporal artery, just in front of the ear.
- Pulse rates at rest are approximately as follows:
 - infants, 140 beats/minute
 - adults, 60–80 beats/minute.
- Pulse rate is increased in:
 - exercise
 - anxiety
 - fear
 - some cardiac disorders
 - hyperthyroidism and other disorders.
- The rhythm should be regular; if not, ask a physician for advice. The character and volume vary in certain disease states and require a physician's advice.

- **The blood pressure:** this can be measured with a sphygmomanometer, or one of a variety of machines. With a sphygmomanometer the procedure is as follows: seat the patient; place the sphygmomanometer cuff on the right upper arm, with about 3 cm of skin visible at the antecubital fossa; palpate the radial pulse; inflate the cuff to about 200–250 mmHg or until the radial pulse is no longer palpable; deflate the cuff slowly while listening with the stethoscope over the brachial artery on the skin of the inside arm below the cuff; record the systolic pressure as the pressure when the first tapping sounds appear; deflate the cuff further until the tapping sounds become muffled (diastolic pressure); repeat; record the blood pressure as systolic/diastolic pressures (normal values about 120/80 mmHg, but these increase with age).

Other signs

- **Weight:** weight loss is seen mainly in malnutrition, eating disorders, cancer, HIV infection, malabsorption and tuberculosis.
- **Skin:** lesions such as rashes (seen mainly in skin diseases, infections and drug reactions), pigmentation (seen in various ethnic groups, Addison's disease and as a result of some drug therapy).
- **Hands:** conditions such as arthritis (mainly rheumatoid or osteoarthritis) and Raynaud's phenomenon, which is seen in many connective tissue diseases.
- **Nails:** changes such as kollonychia (spoon-shaped nails), as seen in iron deficiency anaemia, and finger clubbing, as seen mainly in cardiac or respiratory disorders.

Extraoral head and neck examination

The face should be examined for lesions and features such as (Table 2.1):

- pallor, seen mainly in the conjunctivae or skin creases in anaemia
- rash, such as the malar rash in systemic lupus erythematosus
- erythema, seen mainly on the face in an embarrassed patient, or fever (sweating or warm hands), and then usually indicative of infection.

Eyes should be examined for features such as:

- exophthalmos (prominent eyes), seen mainly in Graves thyrotoxicosis
- jaundice, seen mainly in the sclerae in liver disease.

Hair problems such as alopecia may be present in some skin disorders.

Inspection of the neck, looking particularly for swellings or sinuses, should be followed by careful palpation of all the lymph nodes and sali-

Table 2.1 The commoner descriptive terms applied to lesions

Term	Meaning
Atrophy	Loss of tissue with increased translucency, unless sclerosis is associated
Bullae	Visible accumulations of fluid within or beneath the epithelium, >0.5 cm
Cyst	Closed cavity or sac (normal or abnormal) with an epithelial, endothelial or membranous lining and containing fluid or semisolid material
Ecchymosis (bruise)	Macular area of haemorrhage >2 cm in diameter
Erosion	Loss of epithelium which usually heals without scarring. It commonly follows a blister
Erythema	Redness of the mucosa produced by atrophy, inflammation, vascular congestion or increased perfusion
Exfoliation	The splitting off of the epithelial keratin in scales or sheets
Fibrosis	The formation of excessive fibrous tissue
Fissure	Any linear gap or slit in the skin or mucosa
Gangrene	Death of tissue, usually due to loss of blood supply
Haematoma	A localised tumour-like collection of blood
Macule	A circumscribed alteration in colour or texture of the mucosa
Nodule	A solid mass in the mucosa or skin which can be observed as an elevation or can be palpated. It is >0.5 cm in diameter
Papule	A circumscribed palpable elevation <0.5 cm in diameter
Petechia (pl. petechiae)	A punctate haemorrhagic spot approximately 1-2 mm in diameter
Plaque	An elevated area of mucosa >0.5 cm in diameter
Pustule	A visible accumulation of free pus
Scar	Replacement by fibrous tissue of another tissue which has been destroyed by injury or disease. An atrophic scar is thin and wrinkled. A hypertrophic scar is elevated; with excessive growth of fibrous tissue. A cribriform scar is perforated with multiple small pits
Sclerosis	Diffuse or circumscribed induration of the submucosal and/or subcutaneous tissues

Contd

Table 2.1 Contd

Term	Meaning
Tumour	Literally a swelling. The term is used to imply enlargement of the tissues by normal or pathological material or cells that form a mass. The term should be used with care, as many patients believe it implies a malignancy with a poor prognosis
Ulcer	A loss of epithelium, often with loss of the underlying tissues, produced by sloughing of necrotic tissue
Vegetation	A growth of pathological tissue consisting of multiple closely set papillary masses
Vesicles	Small (<0.5 cm in diameter) visible accumulations of fluid within or beneath the epithelium
Weal	A transient area of mucosal or skin oedema, white, compressible and usually evanescent

vary and thyroid glands, searching for swelling or tenderness. The neck is best examined by observing the patient from the front, noting any obvious asymmetry or swelling, then standing behind the seated patient to palpate the lymph nodes. Most of the physical examination is undertaken from behind (Fig. 2.1).

The lymph nodes should be examined. Lymph from the superficial tissue of the head and neck generally drains first to groups of superficially

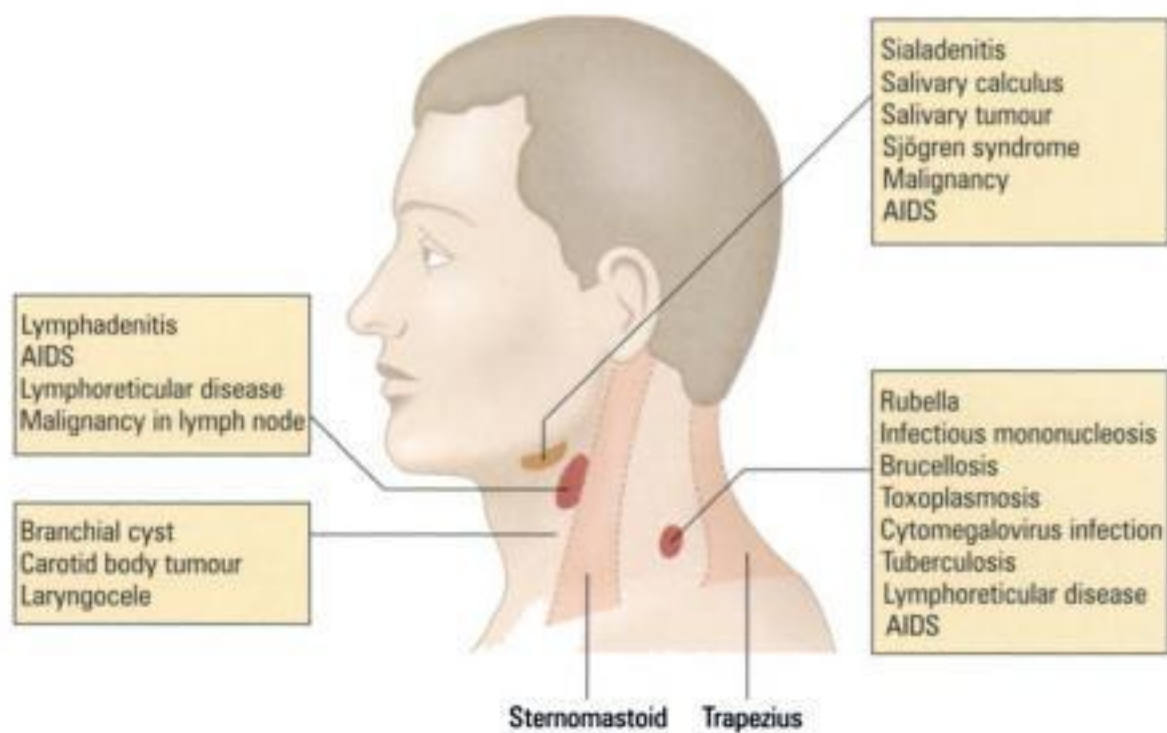


Figure 2.1 Some causes of neck swelling

placed lymph nodes, then to the deep cervical lymph nodes (Figs 2.2–2.4 and Table 2.2). Systematically, each region needs to be examined lightly with the pulps of the fingers, trying to roll the lymph nodes against harder underlying structures:

- Parotid, mastoid and occipital lymph nodes can be palpated simultaneously using both hands.
- Superficial cervical lymph nodes are examined with lighter fingers as they can only be compressed against the softer sternomastoid muscle.
- Submental lymph nodes are examined by tipping the patient's head forward and rolling the lymph nodes against the inner aspect of the mandible.
- Submandibular lymph nodes are examined in the same way, with the patient's head tipped to the side which is being examined. Differentiation needs to be made between the submandibular salivary gland and submandibular lymph glands. Bimanual examination with one finger in the floor of the mouth may help.
- The deep cervical lymph nodes which project anterior or posterior to the sternomastoid muscle can be palpated. The jugulodigastric lymph node in particular should be specifically examined, as this is the most common lymph node involved in tonsillar infections and oral cancer.
- The supraclavicular region should be examined at the same time as the rest of the neck; lymph nodes here may extend up into the posterior triangle of the neck on the scalene muscles, behind the sternomastoid.
- Parapharyngeal and tracheal lymph nodes can be compressed lightly against the trachea.

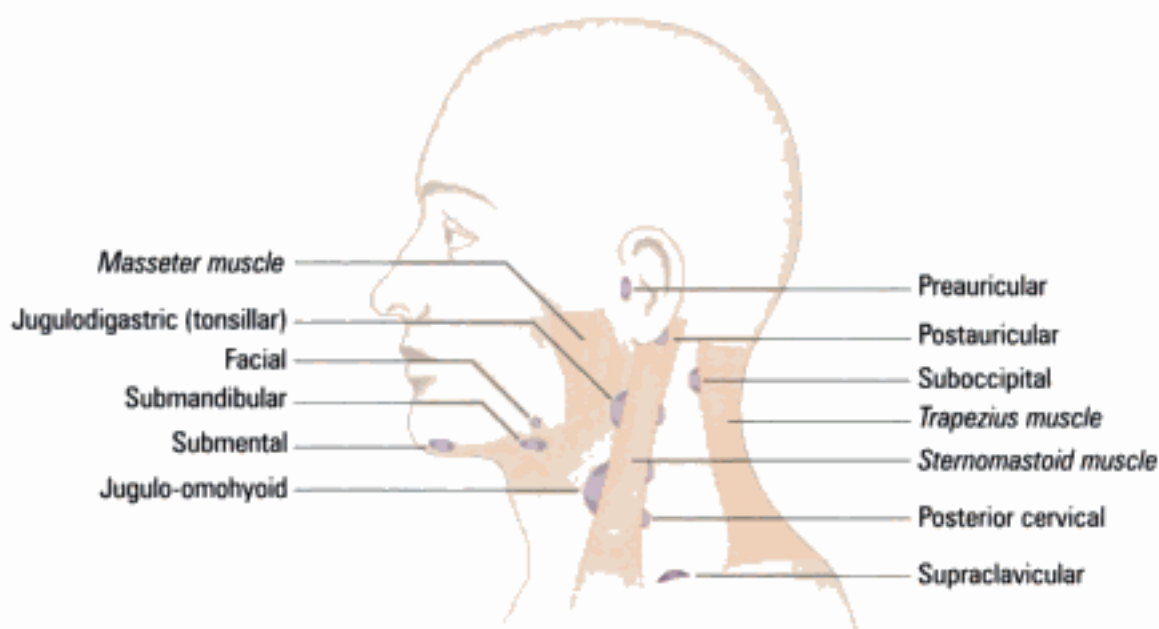


Figure 2.2 Cervical lymph nodes

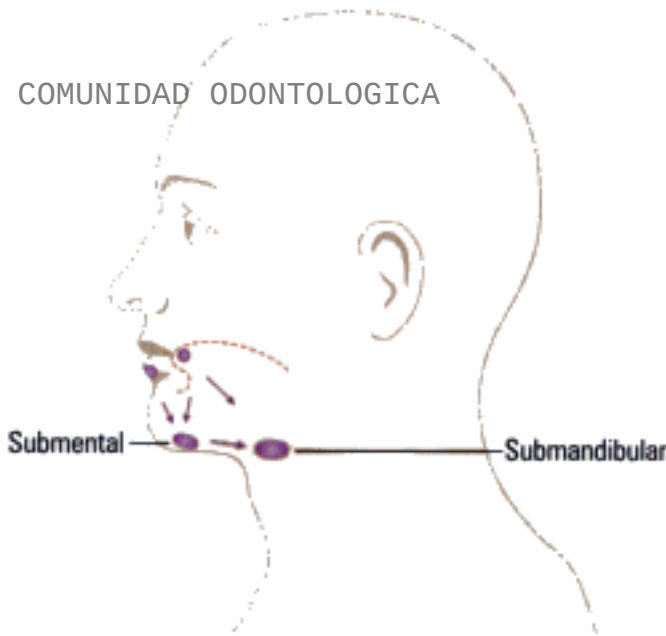


Figure 2.3 Submental and submandibular lymph nodes

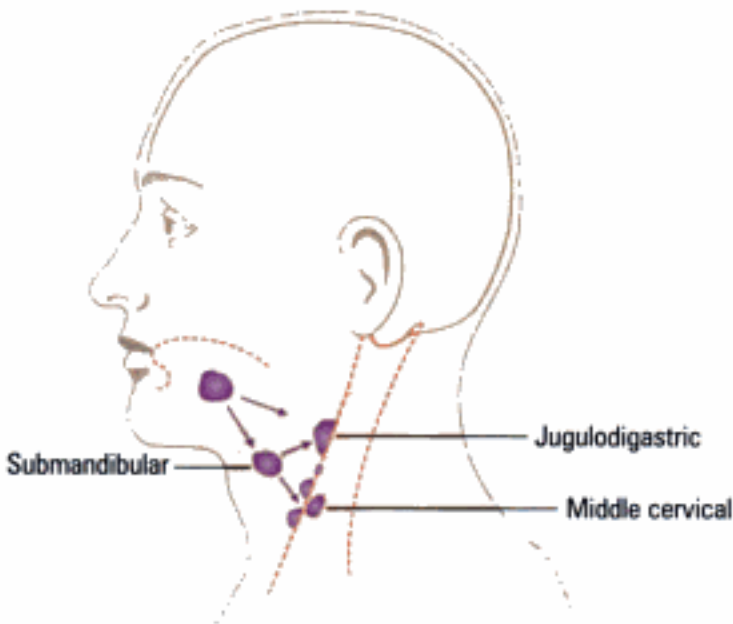


Figure 2.4 Submandibular and deep cervical lymph nodes

- Some information can be gained by the texture and nature of the lymphadenopathy.
- Tenderness and swelling should be documented. Lymph nodes that are tender may be inflammatory (lymphadenitis). Consistency should be noted. Nodes that are increasing in size and are hard, or fixed to adjacent tissues may be malignant.
- Both anterior and posterior cervical nodes should be examined as well as other nodes, liver and spleen if systemic disease is a possibility. Generalised lymphadenopathy with or without enlargement of other lymphoid tissue such as liver and spleen (hepatosplenomegaly) suggests a systemic cause.

Table 2.2 The cervical lymph nodes and their main drainage areas

Area	Draining lymph nodes
Scalp, temporal region	Superficial parotid
Scalp, posterior region	Occipital
Scalp, parietal region	Mastoid
Ear, external	Superficial cervical over upper part of sternomastoid muscle
Ear, middle	Parotid
Over angle of mandible	Superficial cervical over upper part of sternomastoid muscle
Medial part of frontal region, medial eyelids, skin of nose	Submandibular
Lateral part of frontal region, lateral part of eyelids	Parotid
Cheek	Submandibular
Upper lip	Submandibular
Lower lip	Submental
Lower lip, lateral part	Submandibular
Mandibular gingivae	Submandibular
Maxillary teeth	Deep cervical
Maxillary gingivae	Deep cervical
Tongue tip	Submental, remainder drains to submandibular nodes
Tongue, anterior two-thirds	Submandibular, some midline cross-over of lymphatic drainage
Tongue, posterior third	Deep cervical
Tongue ventrum	Deep cervical
Floor of mouth	Submandibular
Palate, hard	Deep cervical
Palate, soft	Retropharyngeal and deep cervical
Tonsil	Jugulodigastric

The temporomandibular joints (TMJ) and muscles of mastication should be examined. Although disorders which affect the TMJ often appear to be unilateral, the joint should not be viewed in isolation but always considered along with its opposite joint, as part of the stomatognathic system. Some practitioners palpate using a pressure algometer to standardise the force used, and undertake range-of-movement (ROM) measurements. The area should be examined by inspecting:

- Facial symmetry, for evidence of enlarged masseter muscles (masseteric hypertrophy) suggestive of clenching or bruxism.
- Mandibular opening and closing paths.
- Mandibular opening extent, measuring the inter-incisal distance at maximum mouth opening.
- Lateral excursions, measuring the amount achievable.
- Joint noises, by listening (a stethoscope placed over the joint can help).
- Both condyles, by palpating them, via the external auditory meatus, to detect tenderness posteriorly, and by using a single finger placed over the joints in front of the ears, to detect pain, abnormal movements or clicking within the joint.
- Masticatory muscles on both sides:
 - Masseters, by intraoral–extraoral compression between finger and thumb. Palpate the masseter bimanually by placing a finger of one hand intraorally and the index and middle fingers of the other hand on the cheek over the masseter over the lower mandibular ramus.
 - Temporalis, by direct palpation of the temporal region. Palpate the temporal origin of the temporalis muscle by asking the patient to clench their teeth. Palpate the insertion of the temporalis tendon intraorally along the anterior border of the ascending mandibular ramus.
 - Lateral pterygoid (lower head), by placing a little finger up behind the maxillary tuberosity (the 'pterygoid sign'). Examine the lateral pterygoid muscle, which cannot readily be palpated, indirectly by asking the patient to open the jaw against resistance and to move the jaw to one side while applying a gentle resistance force.
 - Medial pterygoid muscle, intraorally lingually to the mandibular ramus.
- The dentition and occlusion. This may require monitoring of study models on a semi or fully adjustable articulator. Note particularly missing premolars or molars, and attrition.
- The mucosa. Note particularly occlusal lines and scalloping of the tongue margins which may indicate bruxism and tongue pressure.

Examine the jaws. There is a wide normal individual variation in morphology of the face. Most individuals have facial asymmetry but of a degree that cannot be regarded as abnormal. Maxillary, mandibular or zygomatic

deformities or lumps may be more reliably confirmed by inspection from above (maxillae/zygomas) or behind (mandible). The jaws should be palpated to detect swelling or tenderness. Maxillary air sinuses can be examined by palpation for tenderness over the maxillary antrum which may indicate sinus infection. Transillumination or endoscopy can be helpful.

The major salivary glands should be inspected and palpated (parotids and submandibulars) for:

- facial symmetry
- evidence of enlarged glands
- evidence of salivary flow from salivary ducts
- saliva appearance.

Salivary glands are palpated in the following way:

- Parotid glands are palpated by using fingers placed over the glands in front of the ears, to detect pain or swelling. Early enlargement of the parotid gland is characterised by outward deflection of the lower part of the ear lobe, which is best observed by looking at the patient from behind. This simple sign may allow distinction from simple obesity. Swelling of the parotid sometimes causes trismus. Swellings may affect the whole or part of a gland, or tenderness may be elicited. The parotid duct (Stensen's duct) is most readily palpated with the jaws clenched firmly, since it runs horizontally across the upper masseter where it can be gently rolled; the duct then opens at a papilla on the buccal mucosa opposite the upper molars.
- Submandibular glands are palpated bimanually between fingers inside the mouth and extraorally. The submandibular gland is best palpated bimanually with a finger of one hand in the floor of the mouth lingual to the lower molar teeth, and a finger of the other hand placed over the submandibular triangle. The submandibular duct (Wharton's duct) runs anteromedially across the floor of the mouth to open at the side of the lingual fraenum.

Examine the cranial nerves (Table 2.3). In particular, facial movement should be tested and facial sensation determined. Facial symmetry is best seen as the patient is talking. Movement of the mouth as the patient speaks is important, especially when they allow themselves the luxury of some emotional expression. The upper part of the face is bilaterally innervated and thus loss of wrinkles on one-half of the forehead or absence of blinking suggests a lesion in the lower motor neurone. Examination of the upper face (around the eyes and forehead) is carried out in the following way:

- If the patient is asked to close their eyes the palsy may become obvious, with the affected eyelid failing to close and the globe turning up so that only the white of the eye is showing (Bell's sign).

Table 2.3 Examination of cranial nerves

Cranial nerve		Findings in lesions
I	Olfactory	Impaired sense of smell for common odours (do not use ammonia)
II	Optic	Visual acuity reduced using Snellen types $\pm$ ophthalmoscopy: nystagmus Visual fields by confrontation impaired Pupil responses may be impaired
III	Oculomotor	Diplopia; strabismus; eye looks down and laterally Eye movements impaired Ptosis Pupil dilated Pupil reactions: direct reflex impaired, but consensual reflex intact
IV	Trochlear	Diplopia, particularly on looking down Strabismus No ptosis Pupil normal and normal reactivity
V	Trigeminal	Reduced sensation over face $\pm$ corneal reflex impaired $\pm$ taste sensation impaired Motor power of masticatory muscles reduced, with weakness on opening jaw; jaw jerk impaired Muscle wasting
VI	Abducens	Diplopia Strabismus Lateral eye movements impaired to affected side
VII	Facial	Impaired motor power of facial muscles on smiling, blowing out cheeks, showing teeth, etc. Corneal reflex reduced $\pm$ taste sensation impaired
VIII	Vestibulo-cochlear	Impaired hearing (tuning fork at 256 Hz) Impaired balance $\pm$ nystagmus $\pm$ tinnitus
IX	Glosso-pharyngeal	Reduced gag reflex Deviation of uvula Reduced taste sensation Voice may have nasal tone
X	Vagus	Reduced gag reflex Voice may be impaired
XI	Accessory	Motor power of trapezius and sternomastoid reduced
XII	Hypoglossal	Motor power of tongue impaired, with abnormal speech $\pm$ fasciculation, wasting, ipsilateral deviation on protrusion

- Weakness of orbicularis muscles with sufficient strength to close the eye can be compared with the normal side by asking the patient to close their eyes tight and observing the degree of force required to part the eyelids.
- If the patient is asked to wrinkle their forehead, weakness can be detected by the difference between the two sides.

The lower face (around the mouth) is best examined by asking the patient to:

- smile
- bare the teeth or purse the lips
- blow out the cheeks.

The cranial nerves can be examined further:

- The corneal reflex: this depends on the integrity of the trigeminal and facial nerves, either of which if defective will give a negative response. It is important to test facial light touch sensation in all areas but particularly the corneal reflex. Lesions involving the ophthalmic division cause corneal anaesthesia, which is tested by gently touching the cornea with a wisp of cotton wool twisted to a point. Normally, this procedure causes a blink but, if the cornea is anaesthetic (or if there is facial palsy), no blink follows, provided that the patient does not actually see the cotton wool. If the patient complains of complete facial or hemifacial anaesthesia, but the corneal reflex is retained or there is apparent anaesthesia over the angle of the mandible (an area not innervated by the trigeminal nerve), then the symptoms are probably functional (non-organic).
- Taste: unilateral loss of taste associated with facial palsy indicates that the facial nerve is damaged proximal to the chorda tympani.
- Hearing: hyperacusis may be caused by paralysis of the stapedius muscle and this suggests the facial nerve lesion is proximal to the nerve to the stapedius.
- Lacrimation: this is tested by hooking a strip of Schirmer or litmus paper in the lower conjunctival fornix. The strip should dampen to at least 15 mm in 1 minute if tear production is normal. The contralateral eye serves as a control (Schirmer's test). Secretion is diminished in proximal lesions of the facial nerve, such as those involving the geniculate ganglion or in the internal auditory meatus, or in disorders of exocrine glands, such as Sjögren syndrome.
- Facial sensation: progressive lesions affecting the sensory part of the trigeminal nerve initially result in a diminishing response to light touch (cotton wool) and pin-prick (gently pricking the skin with a sterile pin or needle without drawing blood), and later there is complete anaesthesia.

Intraoral examination

PDFFREE COMUNIDAD ODONTOLOGICA

Few oral diseases are life-threatening, though cancer and pemphigus are obvious exceptions. Most diseases have a local cause and can be recognised fairly readily. Even those that are life-threatening, such as oral cancer in particular, can be detected at an exceedingly early stage. However, even now, oral cancer is sometimes overlooked at examination, and the delay between the onset of symptoms of oral cancer and the institution of definitive treatment still often exceeds 6 months.

Many systemic diseases, particularly infections and diseases of the blood, gastrointestinal tract and skin, also cause oral signs or symptoms which may constitute the main complaint, particularly, for example, in some patients with HIV, leukopenia or leukaemia.

The examination should therefore be conducted in a systematic fashion to ensure that all areas are included. If the patient wears any removable prostheses or appliances, these should be removed in the first instance, although it may be necessary later to replace the appliance to assess its fit, function and relationship to any lesion.

Complete visualisation with a good source of light is essential. All mucosal surfaces should be examined, starting away from the location of any known lesions or the focus of complaint, and lesions recorded on a diagram (Fig. 2.5). The lips should first be inspected. The labial mucosa, buccal mucosa, floor of the mouth and ventrum of the tongue, dorsal surface of the tongue, hard and soft palates, gingivae and teeth should then be examined in sequence (Table 2.4).

- Lips: features such as cyanosis are seen mainly in the lips in cardiac or respiratory disease; angular cheilitis is seen mainly in oral candidiasis or

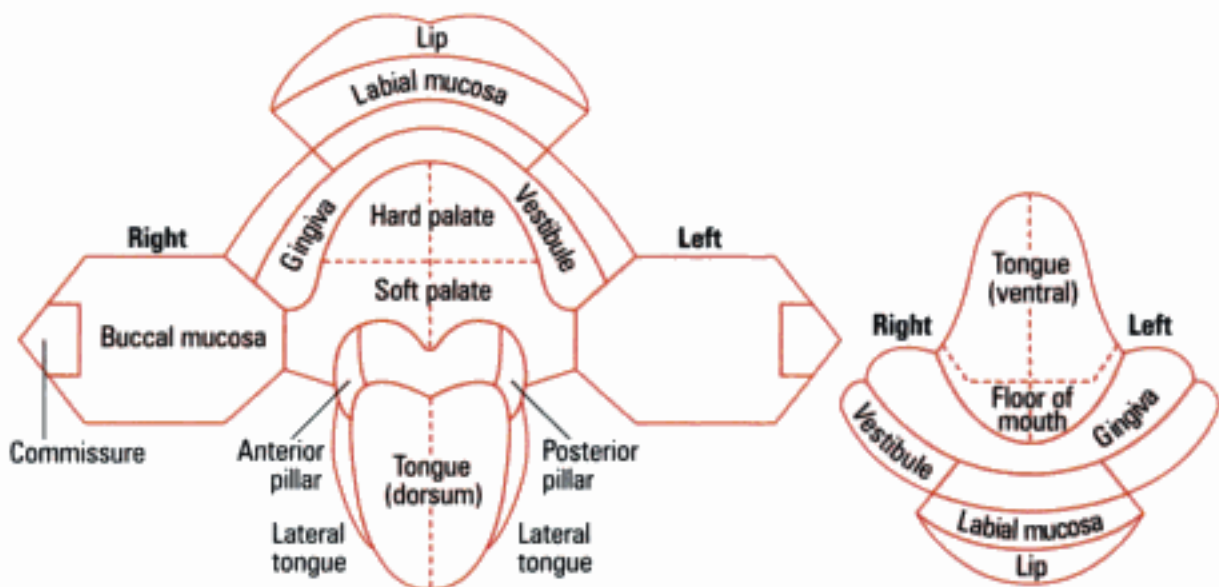


Figure 2.5 Mouth chart

iron or vitamin deficiencies. Examination is facilitated if the mouth is gently closed at this stage, so that the lips can then be everted to examine the mucosa.

- Labial mucosa normally appears moist with a fairly prominent vascular arcade. In the lower lip, the many minor salivary glands which are often exuding mucus are easily visible. The lips therefore feel slightly nodular and the labial arteries are readily felt. Many adults have a few yellowish pinhead-sized papules in the vermillion border (particularly of the upper lip) and at the commissures; these are usually ectopic sebaceous glands (Fordyce spots), and may be numerous, especially as age advances.
- Cheek (buccal) mucosa is readily inspected if the mouth is held half open. The vascular pattern and minor salivary glands so prominent in

Table 2.4 The more commonly used tooth notations

Palmer	
Permanent dentition	Upper 87654321 12345678 Right Left 87654321 12345678 Lower
Deciduous dentition (anonymous classification)	EDCBA ABCDE EDCBA ABCDE
Haderup	
Permanent dentition	(8+)(7+)(6+)(5+)(4+)(3+)(2+)(1+) (+1)(+2)(+3)(+4)(+5)(+6)(+7)(+8) (8-)(7-)(6-)(5-)(4-)(3-)(2-)(1-) (-1)(-2)(-3)(-4)(-5)(-6)(-7)(-8)
Deciduous dentition	(50+)(40+)(30+)(20+)(10+) (+01)(+02)(+03)(+04)(+05) (50-)(40-)(30-)(20-)(10-) (-01)(-02)(-03)(-04)(-05)
Universal	
Permanent dentition	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 32 31 30 29 28 27 26 25 24 23 22 21 20 19 18 17
Deciduous dentition	A B C D E F G H I J T S R Q P O N M L K
Fédération Dentaire Internationale (two-digit)	
Permanent dentition	18 17 16 15 14 13 12 11 21 22 23 24 25 26 27 28 48 47 46 45 44 43 42 41 31 32 33 34 35 36 37 38
Deciduous dentition	55 54 53 52 51 61 62 63 64 65 85 84 83 82 81 71 72 73 74 75

the labial mucosa are not obvious in the buccal mucosa, but Fordyce spots may be conspicuous, particularly near the commissures and retro-molar regions in adults. Place the surface of a dental mirror against the buccal mucosa. The mirror should slide and lift off easily; if it adheres to the mucosa, then xerostomia is present.

- The floor of the mouth and the ventrum of the tongue are best examined by asking the patient to push the tongue first into the palate and then into each cheek in turn. This raises for inspection the floor of the mouth – an area where tumours may start (the coffin or graveyard area of the mouth). Its posterior part is the most difficult area to examine well and one where lesions are most easily missed. Lingual veins are prominent and, in the elderly, may be conspicuous (lingual varices). Bony lumps on the alveolar ridge lingual to the premolars are most often tori (torus mandibularis). During this part of the examination the quantity and consistency of saliva should be assessed. Examine for the pooling of saliva in the floor of the mouth; normally there is a pool of saliva.
- The dorsum of the tongue is best inspected by protrusion, when it can be held with gauze. The anterior two-thirds is embryologically and anatomically distinct from the posterior third, and separated by a dozen or so large circumvallate papillae. The anterior two-thirds is coated with many filiform but relatively few fungiform papillae. Behind the circumvallate papillae, the tongue contains several large lymphoid masses (lingual tonsil) and the foliate papillae lie on the lateral borders posteriorly. These are often mistaken for tumours. The tongue may be fissured (scrotal), but this is usually regarded as a developmental anomaly. A healthy child's tongue is rarely coated, but a mild coating is not uncommon in healthy adults. The voluntary tongue movements and sense of taste should be formally tested. Abnormalities of tongue movement (neurological or muscular disease) may be obvious from dysarthria or involuntary movements, and any fibrillation or wasting should be noted. Hypoglossal palsy may lead to deviation of the tongue towards the affected side on protrusion. Formal taste testing with salt, sweet, sour and bitter should be carried out by applying solutions of salt, sugar, dilute acetic acid and 5% citric acid to the tongue on a cotton swab or cotton bud.
- The palate and fauces consist of an anterior hard palate and posterior soft palate, and the tonsillar area and oropharynx. The mucosa of the hard palate is firmly bound down as a mucoperiosteum (similar to the gingivae) and with no obvious vascular arcades. Rugae are present anteriorly on either side of the incisive papilla that overlies the incisive foramen. Bony lumps in the posterior centre of the vault of the hard palate are usually tori (torus palatinus). Patients may complain of lumps distal

to the upper molars that they think are unerupted teeth but the pterygoid hamulus or tuberosity is usually responsible for this complaint. The soft palate and fauces may show a faint vascular arcade. Just posterior to the junction with the hard palate is a conglomeration of minor salivary glands. This region is often also yellowish. The palate should be inspected and movements examined when the patient says 'Aah'. Using a mirror, this also permits inspection of the posterior tongue, tonsils, oropharynx, and can even offer a glimpse of the larynx. Glossopharyngeal palsy may lead to uvula deviation to the contralateral side.

- Gingivae in health are firm, pale pink, with a stippled surface, and have sharp gingival papillae reaching up between the adjacent teeth to the tooth contact point. Look for gingival redness, swelling, or bleeding on gently probing the gingival margin. The 'keratinised' attached gingivae (pale pink) is normally clearly demarcated from the non-keratinised alveolar mucosa (vascular) that runs into the vestibule or sulcus. Bands of tissue which may contain muscle attachments run centrally from the labial mucosa onto the alveolar mucosa and from the buccal mucosa in the premolar region onto the alveolar mucosa (fraenae).
- Teeth: the dentition should be checked to make sure that the expected complement of teeth is present for the patient's age. Extra teeth (supernumerary teeth) or deficiency of teeth (partial loss (hypodontia; oligodontia) or complete loss (anodontia)) can be features of many syndromes, but teeth are far more frequently missing because they are unerupted or lost as a result of caries or periodontal disease. The teeth should be fully examined for signs of disease, either malformations such as hypoplasia or abnormal colour, or acquired disorders such as dental caries, erosion or abrasion. The occlusion of the teeth should also be checked; it may show attrition or may be disturbed, as in some jaw fractures or dislocation of the mandibular condyles.

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Diagnosis: General Investigations

Accurate diagnosis is the only true cornerstone on which rational treatment can be built.

C Noyek

Investigations

Following history taking and examination, investigations may be required to help make or confirm the diagnosis and prognosis, or sometimes simply to exclude some diagnoses in order to reassure the patient (and partner, family or clinician). Inadequate investigation could lead to a:

- misdiagnosis
- missed diagnosis
- complaint of bad practice
- legal action.

However, superfluous investigations are:

- liable to engender undue anxiety on the part of the patient, partner or relatives
- time-consuming
- expensive
- occasionally associated with adverse effects, or even dangerous.

The following points should be borne in mind with regard to any form of investigation:

- The first principle must be to do no harm.
- Informed consent is required.
- Only an operator adequately skilled in a procedure should perform it.

- Surgical procedures are invasive and this includes venepuncture and biopsy; an oral biopsy is not always a pleasant procedure.

Informed consent

It is the duty of dental staff to ensure they try and help patients understand their condition. Patients commonly complain that they have been ill-informed about their diagnosis, investigations and the results of these. Patients should always be involved in the decision-making about their management. Careful discussion with the patient is the best approach. Other ways to help are by:

- Writing important points down for the patient.
- Using patient information sheets, examples of which are included in this book.
- Offering guidance to other sources of information, such as written material and the Internet.
- Arranging contact with other patients with the same problems, either individually or through a patient self-help group. Patients with serious conditions, such as cancer, pemphigus or Sjögren syndrome, often benefit from this.
- Explaining the condition, diagnosis, investigations, management and prognosis to someone who can act as an advocate. This could be the patient's parents, partner, friend or relatives. This should only be done if appropriate and only with the patient's express consent.

Consent is implied for taking a history and performing relevant clinical examinations. However, investigations are another matter; the dentist must clearly explain the:

- nature
- potential benefit
- possible adverse effects
- problems and advantages of not carrying out the investigations.

These points must be explained clearly to the patient, in a way that can be readily understood. Routine urinalysis is usually accepted as part of medical and insurance examinations though some patients question its use in dentistry. For other procedures, informed consent should always first be obtained. This applies particularly where there are sensitive issues, such as HIV infection, when the patient must be professionally counselled before serotesting is performed. It is also important where there could be adverse effects such as scarring or loss of sensation after a biopsy.

Verbal informed consent is adequate for non-invasive procedures, but for invasive or risky procedures a signed, witnessed and written informed

consent should be obtained. Such signed informed consent is mandatory for all investigations involving operative procedures. Remember that patients are free to decline any or all investigations should they so wish, but it is wise for the clinician to clearly record that decision in writing in the case records.

A patient has the right under common law to give or withhold consent to medical examination of treatment. This is one of the basic principles of healthcare. Patients are entitled to receive sufficient information in a way they can understand about the proposed treatments, the possible alternatives and any substantial risk or risks which may be special in kind or magnitude or special to the patient, so that they can make a balanced judgement. (UK Health Department 19.2.99. HSC 1999/031).

All body fluids and tissues are potentially infectious. Barrier precautions must therefore always be employed in order to prevent transmission of infection to patients or staff during investigations involving body fluids or tissues.

These procedures can often be carried out in general practice but, for a number of reasons, the dental surgeon may elect to refer to a specialist. The same applies to other investigations, particularly where there are sensitive issues such as possible HIV infection, when medical experience or a medical or specialist opinion could be helpful if not essential.

Urinalysis

This is routinely performed with 'dip-sticks'. It may reveal:

- glycosuria, which may suggest diabetes mellitus
- ketonuria, which may be a sign of diabetic ketoacidosis or starvation
- bilirubin or urobilinogen, which may indicate hepatobiliary disorders
- proteinuria, which may be due to menstruation, or indicate renal, urinary tract or cardiac disease
- haematuria, which may be due to menstruation, or indicate renal or urinary tract disease.

Blood testing

Details of the various blood tests commonly used are shown in Table 3.1. During venepuncture, remember:

- The antecubital fossa is most commonly used since veins are usually large and easily seen.
- Blood is withdrawn automatically into a vacutainer. If a syringe is used, withdraw slowly, making sure that there is no air in the syringe. Too rapid removal of blood may cause haemolysis.

Table 3.1 Blood tests

Full blood count One of the laboratory investigations most frequently requested because anaemia and changes in the white blood cell count occur so commonly in a wide variety of diseases. Blood (5 ml) is anticoagulated with dry potassium edetate (EDTA) and should be received in the haematology laboratory within 24 hours. Blood cells are usually counted and sized in automatic blood cell counters. Folate can be assayed on this sample. Blood film is prepared from the same sample if indicated by the history or by the blood count results, for visual inspection of blood cells.

Erythrocyte sedimentation Can be performed on the same sample, and are global rate (ESR) or plasma measurements of non-specific plasma protein changes in viscosity: principally, increases in the concentration of certain globulins, and a fall in the albumin level. The ESR also increases with anaemia.

Coagulation screen Required to diagnose coagulation disorders. Blood (5 ml) is anticoagulated with liquid sodium citrate and should be received in the haematology laboratory within 4 hours (or within 24 hours for warfarin control by the prothrombin time or International Normalised Ratio (INR)).

Ferritin, iron, transferrin, folate and vitamin B₁₂ (cobalamin) levels Useful in the diagnosis of anaemias due to deficiencies. Blood (10 ml) is added to a plain tube, and should be received in the haematology laboratory within 24 hours.

Blood grouping and cross-matching Required prior to blood cell transfusion or major surgery. Blood (10 ml) is added to a plain tube, and should be received in the haematology laboratory within 4 hours.

Blood glucose Estimations require a special tube (sodium fluoride), and are used to diagnose hypoglycaemia or hyperglycaemia, which is often due to diabetes mellitus

Serum urea, creatinine and electrolyte levels These tests require a plain tube (no anticoagulant), and are used to diagnose renal failure (raised urea and creatinine levels) and electrolyte disturbance.

Serum liver function tests These tests require a plain tube and include measurement of bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, albumin and globulin, which are useful in the diagnosis of jaundice, liver and biliary tract disorders.

Serum calcium, phosphate and alkaline phosphatase These tests require a plain tube, and are useful in the diagnosis of metabolic bone disease.

Serology Useful for assay of various antibodies. These require a plain tube.

- If the specimen tube contains anticoagulant, ensure mixing by gently rolling the tube.
- Carefully dispose of the needle in the sharps container.

- Label the blood collection tubes with the patient's name, number, date and time, etc.
- Complete and sign the appropriate request forms and give relevant clinical data, patient's name and number, etc.

Skin testing

Absorption of many substances through the intact skin is poor and variable, but direct application to the surface of the skin is used for patch testing. The epidermal barrier may be overcome either by removing it or by introducing the material directly with a needle into the dermis. Such tests can be extremely valuable, but details of the type of test and the time at which it is read must correspond to the pathological process under consideration. Interpretation of the relevance of results must always be correlated with the clinical picture. All too often evidence adduced from tests is either meaningless or misleading. The following techniques for skin testing are most commonly used.

Epicutaneous tests – patch tests. Patch tests are usually used to detect contact allergy of the delayed hypersensitivity type. They are usually read at 48–72 hours and again up to 1 week, but can also be read at 0.5 hours to detect contact urticaria. At times patch testing may usefully be combined with scratch testing.

Intradermal injection. The injection is made into the superficial layer of the dermis through a fine-bore (26G or 27G) needle with its bevel pointing upwards. The quantity which may conveniently be injected varies from 0.01 to 0.1 ml. Precise measurement of smaller quantities is difficult and requires syringes with especially well-fitting plungers and a micrometer screw gauge. For routine clinical purposes an approximation is sufficient, either 0.05 ml or the amount which just causes a visible weal (0.01–0.02 ml).

The optimal time for reading the reaction varies with the pharmacological agent or the type of immunological reaction. Most such tests are read at either 15–20 minutes or at 48 hours, but it may be important to read the tests at other times, e.g. at 4–12 hours or after 4 days.

The back, and the flexor aspects of the forearms are most conveniently used. A test solution must always be compared with a control solution (e.g. sterile saline) injected in a comparable site at the same time. A positive test may be taken as one which is significantly different from the control. Assessment of what is significant is difficult and varies with the enthusiasm of the tester. Resuscitation equipment and 1 in 1000 epinephrine must be at hand to cope with any untoward allergic reactions.

Prick test. This is a modification of the intradermal injection. A small quantity of the test solution is placed on the skin and a prick made through it with a sharp needle. This should be superficial and not sufficient to draw blood. The size of the weal and flare are measured after 15 minutes. This test gives reproducible results and is convenient for much routine allergy testing. Because of the discrepancy in quantities injected, the testing solutions are made up at different strengths for prick testing and intradermal testing. The intradermal injections of prick test solutions may be dangerous.

Scratch test. The scratch test resembles the prick test. A linear scratch about 1 cm long, but not sufficient to draw blood, is made through the epidermis. This test gives less reproducible results than the prick test.

Modified prick test. Here a drop of the test solution is placed on the skin. A needle is then inserted very superficially and almost horizontally into the skin and lifted to raise a tiny tent of epidermis. This test is slightly more sensitive than the ordinary prick test, but gives no more reproducible results.

Biopsy

Biopsy is the removal of a small piece of tissue from the living body for the purpose of diagnosis by microscopic examination. It is often indicated in order to confirm or make a precise diagnosis, especially in the case of mucosal lesions, when a specimen for immunostaining is often also called for.

Indications for biopsy include (Table 3.2):

- lesions which have neoplastic or premalignant features or are enlarging
- persistent lesions that are of uncertain aetiology
- persistent lesions that are failing to respond to treatment
- confirmation of the clinical diagnosis is required
- lesions that are causing the patient extreme concern.

Biopsy technique

Tissue may be obtained by two main methods: techniques not requiring anaesthesia (e.g. exfoliative cytology and brush biopsy) and techniques requiring local anaesthesia. Those requiring local anaesthesia include:

- scalpel or tissue punch – incisional biopsy
- scalpel or laser cutting – excisional biopsy
- curettage
- needle biopsy, these include:

cutting biopsy using a 14G Tru-Cut needle, which is wide bore
cutting biopsy using a 16G Vim Silverman needle
fine-needle cutting biopsy (FNCB) using an 18G TSK Surecut needle
fine-needle aspiration biopsy (FNA or FNAB) or cytology (FNAC)
using a 22G or 25G standard disposable needle, sometimes as
ultrasound-guided fine-needle aspiration cytology (US-FNAC).

In the case of suspected potentially malignant or malignant mucosal lesions it can be difficult to decide exactly which is the part of the lesion that is best biopsied. Most significant information can be gained from red mucosal areas (erythroplasia) rather than white areas (leukoplakia) and it can be helpful to stain the mucosa before biopsy with toluidine blue dye (vital staining), which is taken up by nuclei and stains pathological areas mainly, causing suspect mucosal areas to stain blue. The technique is of limited value in a primary care setting but may have a place in the hands of an experienced clinician, in high-risk patients. The usual procedure is as follows: the patient is asked to rinse for 20 seconds with a solution of 1% acetic acid to cleanse the area of mucus, etc.; they then rinse for 20 seconds with plain water; they then rinse for 60 seconds with 1% aqueous toluidine blue solution; they then rinse for 20 seconds with a 1% solution of acetic acid; and finally they rinse for 20 seconds with water.

Table 3.2 Main indications for biopsy

Lesions which have neoplastic or premalignant features or are enlarging	Erythroplakia Leukoplakia Lichen planus Focal pigmented lesions Lumps
Persistent lesions of uncertain aetiology	Soft or hard tissue
Persistent lesions failing to respond to treatment	Ulcers or lesions, such as some radiolucent or radio-opaque bone lesions
Persistent focal lesions involving the gingival/periodontium	Non-healing extraction sockets
Confirmation of clinical diagnosis	For example, labial salivary gland biopsy to confirm Sjögren syndrome
Lesions causing the patient extreme concern	Patients may prefer the biopsy or excision biopsy of a persistent red, white or pigmented lesion or lump

Patient information sheet**POST-BIOPSY CARE**

- A biopsy is the taking of a small piece of tissue for microscopic examination.
- This is carried out usually after a local anaesthetic injection in the area, such as used for fillings.
- Biopsy is painless, though a little sore when the injection wears off after a couple of hours.
- Stitches may or may not be used.
- Stitches may be resorbable or need to be removed in the next week. It is usually not a problem if the stitches come out earlier than 1 week.
- Any interventional procedure may occasionally result in complications, such as a little:
 - bleeding: pressure for 5–10 minutes from a gauze swab will almost invariably stop the bleeding
 - soreness or pain: paracetamol/acetaminophen will usually control any discomfort; aspirin should not be used as it can cause bleeding
 - swelling: this should subside spontaneously over 3–4 days
 - bruising: this should clear spontaneously over 4–5 days.
- Rarely there may be:
 - altered sensation
 - restricted mouth opening
 - reactions to drugs
 - allergies
 - infection.
- If you are at all concerned, for advice kindly telephone
- However, there are usually no long-term consequences. The scar is usually almost invisible, any discomfort goes quickly and any slight numbness recovers.

Usually a single biopsy is taken, but multiple biopsies may be indicated where:

- additional investigations such as immunostaining are required
- malignant disease is suspected
- there are widespread leukoplakic or erythroplakic field changes (such biopsies may be termed 'geographic' biopsies).

Biopsy procedure

Informed consent is mandatory for biopsy as for all operative procedures, particularly noting any possible adverse effects, such as postoperative pain or loss of sensation. Care must be taken not to produce anxiety where it is not necessary; some patients equate biopsy with a diagnosis of cancer.

Complete the request form with the:

- patient's full name
- patient's date of birth
- hospital number, if applicable
- date
- site of biopsy
- clinical résumé
- dates, and numbers, of all previous biopsies.

The container must be labelled clearly with:

- patient's full name
- patient's date of birth
- number
- date
- specimen site.

Mucosal biopsies

Mucosal biopsies are *excisional* (removal of the complete lesion) and undertaken with a scalpel, or *incisional* and taken with a scalpel or biopsy punch, usually under local analgesia. Excisional biopsy is preferred for small, isolated and probably benign lesions.

The biopsy should include lesional and normal tissue and should be large enough to handle, and to provide adequate information about the lesion. In the case of ulcerated mucosal lesions, most histopathological information is gleaned from the perilesional tissue, since by definition most epithelium is lost from the ulcer itself. The punch has the advantages for incision biopsy that:

- the incision is controlled
- an adequate specimen is obtained (typically 4 or 6 mm in diameter)
- the patient is not disturbed by the sight of a scalpel
- suturing may not be required.

However, only a fairly small biopsy is obtained with the punch and, in some instances, a larger piece of tissue is needed, or the whole lesion is to be removed, when the scalpel has advantages, particularly when the lesion is on the gingivae, especially lingually or other areas in which it is difficult to gain access with a punch or when mucosa is fragile (e.g. pemphigus). A number 15 blade is usually chosen.

To carry out a biopsy:

- A local analgesic should be given.
- Ensure tissue representative of the lesion is obtained. In mucosal lesions, include some normal tissue as well as the lesion (biopsies of ulcers

alone are inadequate). When a vesiculobullous disorder is suspected, include perilesional tissue and use a scalpel rather than a punch.

- Do not squeeze with forceps as this can cause crush artefacts. Sutures may be used to hold the tissue and also to mark specific areas of biopsy.
- Place the biopsy specimen onto a small piece of paper before immersing in fixative, as this prevents curling. Put small specimens for histological examination immediately into buffered formalin or other fixative in at least its own volume of fixative, preferably ten-fold more, and leave at room temperature. A further biopsy specimen (or half of a larger biopsy) should also be immediately snap-frozen if immunostaining or a frozen section is required. If bacteriological examination is required, for example in suspected tuberculosis, send a separate specimen without fixative.
- Suture if necessary, preferably using a fine needle and resorbable suture such as Vicryl Rapide 4/0, which will not require the patient to re-attend for removal. Non-resorbable sutures such as silk are also available.
- Use of an inverted suture technique means that there is no knot left in the mouth to irritate the patient.

Immunostaining and immunofluorescence

Specimens for immunostaining should not be fixed in formalin, but must be handed immediately to laboratory staff for freezing, or immediately snap-frozen (on solid carbon dioxide or liquid nitrogen) and taken within an hour or so to the laboratory, or, occasionally put into Michel's solution if the specimen cannot be frozen.

- Direct immunofluorescence is a qualitative technique used to detect immune deposits (antibodies and/or complement) in the tissues. It is a one-stage technique, requiring patient lesional or perilesional tissue. Immunostaining usually uses a fluorescein stain which fluoresces apple green under ultraviolet light, and is termed 'immunofluorescence'. It is useful in the diagnosis particularly of vesiculobullous disorders such as pemphigoid and pemphigus.
- Indirect immunofluorescence is a qualitative and quantitative technique used to detect immune deposits (circulating antibodies and/or complement) in the serum. It is a two or more stage technique requiring patient serum and animal tissue.

Oral smears for cytology

Prepared in this way, smears will keep for up to 3 weeks:

- Take smears with a wooden or metal spatula, or dental plastic instrument.
- Spread smears evenly on the centres of two previously labelled glass slides.

- Fix smears immediately in industrial methylated spirit. Do not allow to dry in air as cellular detail is rapidly lost and artefacts develop.
- After 20 minutes of fixation the smears can be left to dry in the air or left in fixative.

Oral brush biopsy

The brush biopsy is performed without anaesthetic and using a brush designed to obtain a transepithelial specimen containing cells from all three layers of the epithelium: the basal, intermediate, and superficial layers. This feature distinguishes it from cytology which samples cells only from the surface of a lesion. It is important to ensure that the brush penetrates to the basement membrane since the basal cell layer may be the only layer of the epithelium that contains abnormal cells within a potentially malignant or malignant lesion. This objective can be achieved by applying firm pressure when performing the brush biopsy procedure and rotating the brush on the lesion approximately five to ten times, visualising pinpoint bleeding or a pinkish-red mucosa at the site of the brush biopsy. The laboratory evaluates the specimen for adequacy by verifying cellular representation from each layer of the epithelium. The computer does not give a final diagnosis but assists in the identification and display of potentially abnormal cells, which are reviewed by pathologists.

Lymph node

Lymph nodes should not be subjected to open biopsy if malignant disease is suspected: FNAB or FNAC are better, or the biopsy deferred until the time of operation.

Labial salivary gland

- Warn the patient of possible postoperative mild hypoaesthesia.
- Give the patient local analgesia.
- Make a linear mucosal incision about 5–8 mm long (to one side of the midline in the lower labial mucosa, towards the sulcus) or an X-shaped incision over the swelling which overlies the salivary gland.
- Excise at least four lobules of salivary gland.
- Suture the wound if necessary.

Frozen sections for rapid diagnosis

This procedure, in which the section is examined whilst the patient is still under anaesthesia, is useful in cases where malignancy is suspect and in resections, to check the resection margin for tumour infiltration and to assess whether the margins are tumour-free.

Communicate with the pathologist at the latest by the day before the operation. Specimens should be immediately snap-frozen (on solid carbon

dioxide or liquid nitrogen) and taken immediately to the laboratory, or collected by the pathology team. Telephone the laboratory when the specimen is on its way. Warn the pathologist about any tissue containing calcified material that could break the microtome. The results should be phoned by the pathologist to the clinician direct.

Imaging

Because of the adverse effects of ionising radiation and the cumulative effect of radiation hazard, all investigations using x-rays must be justified by benefiting the patient. The clinician requesting the examination or investigation must satisfy himself that each investigation is necessary and that the benefit outweighs the risk.

Radiological and some other imaging tests often involve radiation exposure which, even if not serious, often worry the patient. Ionising Radiation Regulations (1988) required exposure of patients to be 'As Low As Reasonably Achievable' (ALARA) and have been superseded by the Ionising Radiation Regulations (1999) (IRR99) and Ionising Radiation (Medical Exposure) Regulations (2000) (IR(ME)R2000).

Radiography

The request form for radiography should be completed and signed by the clinician and should include:

- Vital patient data: full name, address, age, unit number, ward or outpatient department and specialist in charge.
- Details that facilitate correct investigations and accurate opinion:
 - investigations required (region to be examined and, where relevant, special investigation needed)
 - diagnostic problem
 - relevant clinical features
 - known diagnoses
 - previous relevant operations.
- Other information, for example, whether the patient is a walking or trolley case, whether an urgent or routine report is required, the date, place and type of previous radiographs.

A protective lead apron having a lead equivalence of no less than 0.25 mm is worn by the patient only where the primary x-ray beam can strike the pelvis, such as in vertex-occlusal radiography, and a neck shield is indicated if the thyroid is to be exposed.

A particular problem arises during pregnancy, because of the hazard to the foetus. Enquiry as to pregnancy must always be made (risk of foetal irradiation) before performing radiography or other imaging procedures

Table 3.3 Investigative procedures in diseases of the jaws and sinuses

Procedure	Advantages	Disadvantages	Remarks
Transillumination	Simple	-	Helpful to show a fluid level
Fibre-optic endoscopy	Simple; good visualisation	Skill needed	Useful to examine nasal passages, pharynx and larynx
Radiography	Reveals much data not obvious on clinical examination	Specialised techniques may be difficult	Upper occlusal radiography is useful for detecting cysts. Other radiographic views may fail to show cysts and diagnosis of a cyst can be very difficult if the antrum is large with outpouchings into the alveolar process and zygomatic bone, since these antral extensions may resemble cysts. Occipitomental radiography (Waters) views of the skull are the best radiographs for viewing the antra. These views can be taken at 15° and 30° These radiographs show an opaque antrum, a fluid level or fractures

Computerised axial tomography (CAT scan) and magnetic resonance imaging (MRI)	Reveal data often not seen on clinical or conventional radiographic examination	Expensive and not universally available. Interpretation requires additional training	Demonstrate both hard and soft tissues and give spatial relationships. Coronal computed tomography of the antrum can be useful for showing the extent of a neoplasm, particularly in the posterior and superior maxilla. CAT and MRI are useful particularly in detecting the extent of spread of a malignant neoplasm of the antrum. They have the great advantage of demonstrating the posterior maxilla, the intratemporal fossa, the floor of the orbit and the nasoethmoidal sinuses – sites not readily seen
Aspiration of cystic lesion	Simple	May introduce infection	May show the presence of haemangioma. The protein content of cyst fluid may be of diagnostic value (protein levels below 4 g% in keratocysts)
Bone biopsy	Definitive	Invasive	
Bone scan	Surveys all skeleton	Those of any isotope procedure	May reveal pathology (e.g. metastases or osteomyelitis)

which involve radiation exposure by the primary beam to the abdomen and pelvis. Although most dental radiography does not constitute a risk, the clinician should always ascertain whether a woman is pregnant before requesting a radiograph and the investigation required should be discussed with the patient, who may wish to defer it until after pregnancy.

Note whether the patient:

- is of child-bearing potential
- is taking the contraceptive pill
- has had a hysterectomy
- has been sterilised.

Restricting x-ray investigations on women of child-bearing age to the 10 days following the start of a menstrual period (the 10-day rule) should be considered only for examinations with a relatively high gonad radiation risk, and has now fallen somewhat into disfavour.

Portable x-rays

- The quality of portable films is rarely as good as that of corresponding films taken using non-portable equipment.
- Examination should take place in the ward only if there is an absolute contraindication to the patient being brought to the department. If there is any doubt about the advisability of bringing the patient to the department, consult a radiologist.
- Theatre radiography is done only when its results are needed during the operation.

Table 3.4 Investigative procedures in temporomandibular joint disease

Procedure	Advantages	Disadvantages
Radiography	Simple Can reveal much pathology	-
CAT scan	Can provide excellent information	Expensive
Arthrography (double contrast)	Provides excellent information	Danger of introducing infection Painful
Magnetic resonance imaging (MRI)	Provides excellent information without exposure to ionising radiation	Non-invasive Expensive and not universally available
Arthroscopy	Minimally invasive Good visualisation	Requires anaesthesia Technically demanding

Plain radiography

This is useful in the diagnosis of fractures, dislocations, bone and tooth disorders, joint disease and foreign bodies.

Intra-oral radiography

- Periapical radiographs are useful for demonstrating pathology in the periapical region (abscess, granuloma, cyst, etc.) and in tooth root and adjacent bone.
- Bitewing radiographs show both upper and lower premolar and molar teeth on one film but do not show the tooth apex. They are useful for revealing approximal caries and demonstrating the alveolar crest.
- Occlusal films may be useful in assessing the facial and lingual cortices.

Dental panoramic tomography (DPT) (or orthopantomography (OPTG))

This is valuable as a general survey and shows the antra and temporomandibular joints, and the radiation dose is considerably lower than a full mouth survey using periapical films, but it:

- lacks the detail obtained by other films such as periapical radiography
- does not show detail in the anterior jaws
- does not show caries until this is advanced
- can result in ghost shadows and blurring
- examines only a slice of tissue.

Radiovisiography

Radiovisiography (RVG) is digital imaging, and is useful in reducing the radiation exposure, particularly where there is a need for repeated films, such as in endodontics.

Sialography

Sialography involves injection of radio-opaque contrast media into the salivary duct followed by oblique lateral and postero-anterior (PA) or rotated PA radiographs. Use of a sialogogue such as lemon juice to empty the gland gives an 'emptying film'. Sialography can sometimes help to:

- assess patients with xerostomia
- assess patients with salivary swelling
- detect ductal obstruction
- detect the rare cases of salivary aplasia.

Arthrography

Arthrography involves injection of radio-opaque contrast media (usually iohexol or iopamidol) into the lower space of the temporomandibular joint. The main indication is in suspected internal joint derangements.

Table 3.5 Investigative procedures in salivary gland disease

Procedure	Advantages	Disadvantages
Sialometry* (salivary flow rates)	Simple rapid clinical procedure which may confirm or refute xerostomia	Somewhat imprecise Wide range of normal values
Sialochemistry	Laboratory investigation; useful mainly in Sjögren's syndrome	Salivary composition varies with many factors Far less useful than blood and other tests
Blood tests	Simple and can reveal systemic disease (e.g. rheumatoid arthritis)	Will not usually reflect local disease of salivary glands
Plain radiography	Lower occlusal and oblique lateral or OPT may show submandibular calculi Soft PA film may show parotid calculi	Calculi may not be radio-opaque Sialography may be needed
Sialography	Useful to eliminate gross structural damage to calculi or stenoses	Time consuming and somewhat crude and insensitive May cause pain or, occasionally, sialadenitis† Uses x-rays
Salivary gland biopsy	Labial gland biopsy is simple and may reflect changes in other salivary (and exocrine) glands	Invasive

	Major gland biopsy may be diagnostic in localised gland disease Needle biopsy may be useful	Major gland biopsy may result in facial palsy or salivary fistula
Scintigraphy and radiosialometry	Measures uptake of radionuclide* (radiosialometry more quantitative) High uptake (hotspots) may reveal tumours	Expensive and with hazards associated with use of radionuclides Taken up by thyroid gland; rare instances of thyroid damage
Magnetic resonance, CAT scanning, ultrasound	Useful for investigating space-occupying lesions	Expensive, and not universally available

*Unstimulated whole salivary flow rates are usually used; flow rates of less than 1.5 ml/15 min are low. Alternatively, stimulate parotid salivary flow with 1 ml 10% citric acid on to tongue; flow rates of less than 1 ml/min may signify reduced salivary function. Alternatively, pilocarpine 2.5 mg i.v. may be used, but is contraindicated in cardiac patients or those with hypertension. Most centres use citric acid stimulation

*Combined sialography with CAT scanning may be useful in the diagnosis and localisation of salivary gland lesions, particularly parotid neoplasms

*Usually technetium pertechnetate

Table 3.6 Investigative procedures in oral mucosal disease

Procedure	Advantages	Disadvantages	Remarks
Biopsy	Gives definitive diagnosis in many instances	Invasive	Mucosal biopsies should be submitted for histopathological and often direct immunofluorescence examinations if a vesiculobullous disorder is suspected
Brush biopsy	Simple, non-invasive procedure	Possible false-negative results	Helpful in review of widespread possible premalignant lesions
Bacteriological smear and culture	Simple clinical procedure	Isolation of organisms does not necessarily imply causal relation with disease under investigation	Anaerobic techniques may be indicated in oral lesions in the immunocompromised host
Fungal smear	Simple clinical procedure	As above	<i>Candida</i> hyphae suggest <i>Candida</i> species are pathogenic

Viral culture	Simple sensitive clinical procedure Often gives diagnosis more rapidly than does serology*	May require special facilities and may only give retrospective diagnosis	False-negative results possible Indicated in some acute ulcerative or bullous lesions Serology should also be undertaken
DNA studies	Polymerase chain reaction often used	May require special facilities	Rapid and specific results
Haematological screen, haemoglobin red cell and white cell indices	Simple clinical procedure	Detection rate may not be high	Essential to exclude systemic causes of oral disease, especially ulcers, glossitis or angular stomatitis
Serology	Demonstration of a rise in titre-specific antibodies between acute and convalescent serum may be diagnostically useful Specific tests available, e.g. HIV antibodies	Serum autoantibodies may not mean disease Serum autoantibodies may be undetected in pemphigoid Diagnosis of viral infections is retrospective	Essential in suspected HIV, connective tissue disease, autoimmune or other immunological disorders

*Electron microscopy gives the quickest results

Angiography

Angiography involves injection of radio-opaque contrast media into arteries (arteriography) or veins (venography). The main indications for arteriography include:

- diagnosis of vascular anomalies or tumours
- assessment of tumours in the deep lobe of the parotid gland
- assisting surgical procedures (e.g. microvascular surgery or embolisation).

Computed axial tomography

Computed axial tomography (CAT or CT) integrates information from multiple radiographic 'slices' into images of internal tissues (e.g. brain, orbit, sinuses, neck). It:

- has considerable advantages for visualising complex anatomical areas inaccessible to conventional radiographs
- is particularly useful for assessing pathology in the head and neck, especially for determining tumour spread, to exclude cranial base or intracranial pathology and planning surgery and implant placement
- is good for visualising hard tissue lesions
- gives a fairly high radiation exposure (CT of the head can give the equivalent exposure to about 100 chest radiographs)
- is expensive.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) does not involve ionising radiation but depends on the distribution of protons (hydrogen nuclei) in tissues and their effect on a magnetic field. The MRI signal has two components:

- T1, in which the proton is spinning under magnetic influence and radiofrequency to return to the original value (spin lattice or longitudinal relaxation time)
- T2, which depends on the gradual dephasing of the protons in the transverse or transaxial plane (spin-spin, or transverse relaxation times).

The advantages of MRI are that it is:

- especially good for visualising soft tissues and soft tissue lesions
- useful for imaging the temporomandibular joint
- good for revealing bone invasion.

The disadvantages of MRI are that it is:

- not good for imaging bone

Table 3.7 Imaging available for lesions in different locations

Location of lesions	Plain radiography	Other imaging
Mandible	Rotational tomography Oblique lateral CT	MRI Bone scan
Mandibular condyle	Reverse Towne's Submentovertex CT	MRI Bone scan
Temporomandibular joint	Rotational tomography Transcranial CT Transpharyngeal CT	MRI Arthrography Bone scan
Maxilla	30° occipitomeatal CT	MRI Bone scan
Paranasal sinuses	OM rotational tomography for maxillary antra Upper occlusal or lateral Submentovertex CT	MRI Bone scan
Skull	PA skull rotational tomography 10° occipitomeatal Lateral skull CT	MRI Bone scan
Salivary glands	Oblique lateral Rotated PA CT	Sialography Scintigraphy Ultrasound MRI
Intra-oral	Rotational tomography CT	Ultrasound MRI

- fraught with producing image artefacts where metal objects are present (dental restorations, metallic foreign bodies, joint prostheses, etc.)
- expensive.

Contraindications to the use of MRI include:

- implanted electric devices, such as pacemakers, nerve stimulators, cochlear implants
- intracranial vascular clips, if these are ferromagnetic
- prosthetic cardiac valves containing metal.

Thus MRI gives sensitive images of the internal organs and tissues (e.g. brain or spine), but it cannot be used in the presence of metal (e.g. orthodontic fixed or removable appliances or metal-containing prostheses).

Ultrasound (US) scanning

- This involves high frequency sound waves (2–15 MHz) with wavelengths of 0.6–0.01 mm, and does not involve ionising radiation exposure.
- When the sound strikes the interface between media, the energy reflects as an echo, which may be displayed as a unidimensional wave image (an A scan) or, when a sweeping beam is used, as a two-dimensional monochrome image (a B scan).
- Abrupt impedance occurs with calcified lesions, or foreign bodies such as glass or metal.
- Ultrasound therefore gives useful imaging of soft tissues and internal organs (e.g. lymph nodes or salivary glands) and foreign bodies. Colour Doppler ultrasound (CDUS) may be useful.
- Doppler ultrasound is also useful for investigating vascular disease.

Table 3.8 Significance of the more common autoantibodies

Autoantibody	Significance*
DNA antibodies (ds-DNA (<i>Crithidia luciliae</i>))	Systemic lupus erythematosus
Nucleolus-specific RNA	Scleroderma
Sc1-70 (anti-topoisomerase)	Scleroderma
Rheumatoid factor	Rheumatoid arthritis (RA) (sometimes systemic lupus erythematosus)
Robert (Ro), also known as soluble substance A antigen (SS-A)	Sjögren syndrome
Lane (La), also known as soluble substance B antigen (SS-B)	Sjögren syndrome
Epithelial intercellular cement (desmoglein)	Pemphigus
Epithelial basement membrane zone (e.g. integrin)	Pemphigoid
Parietal cell antibody; intrinsic factor antibodies	Pernicious anaemia

*The presence of autoantibodies does not always indicate disease

Chest radiographs

The chest radiograph is valuable in investigating chest disease, heart disease (e.g. heart failure) and general medical problems such as malaise, fever or weight loss (e.g. bronchial carcinoma, tuberculosis and other chest infections).

Abdominal radiographs

Abdominal radiographs are valuable in the diagnosis of gastrointestinal obstruction or perforation, renal stones or gallstones.

Scintiscanning (isotope scanning)

Radioactive pharmaceuticals with affinity for specific organs or tissues can be detected and measured by a gamma camera.

Salivary scintigraphy

Intravenous sodium pertechnetate is taken up by salivary glands and secreted in saliva. Scintiscanning can be useful in the diagnosis of:

- Sjögren syndrome
- ductal obstruction
- salivary neoplasms
- salivary aplasia.

Bone scans

Intravenous technetium methylene diphosphonate is taken up by osteoblasts, and bone scans can be useful in:

- assessing condylar or coronoid hyperplasia
- detecting metastases
- detecting bone invasion
- determining activity on fibro-osseous disease.

Positron emission tomography

Positron emission tomography (PET) produces maps of brain metabolic activity based either on blood flow or glucose utilisation.

Thermography

An infrared camera detects areas of changed vascularity but has the disadvantage of needing the patient to be 'precooled'.

Photography

This is exceedingly useful to record lesions, and the advent of digital photography has considerably improved the quality.

Investigations of specific medical problems

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Anaemia

Anaemia is caused mainly by:

- reduced erythropoiesis
- haemolysis
- haemorrhage.

The most usual cause of anaemia in the developed world is iron deficiency caused by chronic haemorrhage (commonly menorrhagia). After a thorough history and examination, the following are required for diagnosis of the extent and type of anaemia:

- haemoglobin concentration
- a full blood film
- red cell indices
- white cell count and differential.

The cause must then be established.

Deficiency anaemias

Once the type of anaemia has been established, the cause must be found and treated. In iron deficiency, unless it is clear that menorrhagia is the cause, the site of blood loss should be sought, usually in the gastrointestinal tract.

- Iron deficiency anaemia is usually microcytic (mean corpuscular volume (MCV) reduced) and managed by treatment of the cause and iron supplements. Only rarely is transfusion necessary, usually when the haemoglobin is less than 9 g/dl and surgery is required urgently. Packed red cells should be used in preference to blood.
- Folate deficiency is commonly dietary in origin. Folate or vitamin B₁₂ deficiencies may result in a macrocytic (megaloblastic) anaemia (MCV raised). Treatment of folate deficiency is with folic acid.
- Vitamin B₁₂ deficiency is rarely dietary in origin; more commonly, it is caused by a gastrointestinal lesion or pernicious anaemia. Treatment is with vitamin B₁₂, usually by injection for life.
- Deficiencies of multiple haematinic factors, e.g. iron, folate and vitamin B₁₂, may well be caused by disease of the small intestine, such as coeliac disease (gluten-sensitive enteropathy).

Sickle cell anaemia

Sickle cell anaemia is:

- a hereditary condition affecting haemoglobin (sickle haemoglobin (HbS))

- characterised by the fact that the red blood cells may adopt a sickle shape
- found mainly in black patients and some originating from the Mediterranean countries and Asia
- a risk for general anaesthesia.

Rule out sickle cell anaemia in all black patients and record results to prevent unnecessary re-testing.

- Check the medical history.
- Do a full blood picture.
- Do a screening test, such as a simple solubility test (e.g. the SickDex test). This will detect the presence of any HbS in the blood and is therefore positive both in patients with sickle cell anaemia and the trait (see below).
- Further haematological examination, including haemoglobin electrophoresis, is theoretically required for confirmation. In practice, however, a positive solubility test with a low haemoglobin level can be taken as being diagnostic of sickle cell anaemia. A positive solubility test with a normal haemoglobin level may indicate the trait (see below).

Homozygous form: sickle cell anaemia

In the homozygous form, at low oxygen tensions (about 45 mmHg), the red cells become inelastic and sickle shaped. The erythrocytes then either 'sludge', blocking capillaries and causing infarcts (e.g. in bone and brain), or rupture, causing haemolytic anaemia.

Heterozygous form: sickle cell trait

In patients with the sickle trait, sickling occurs only at much lower oxygen tensions (below 20 mmHg), which are unlikely to occur in normal clinical practice.

Bleeding tendency

Screening tests typically include:

- platelet count
- function tests
- APTT (activated partial thromboplastin time)
- PT (prothrombin time) and international normalised ratio (INR)
- clotting factor assays.

Screening tests will eliminate two-thirds of suspected cases, and the remaining third will require more detailed tests to accurately define a diag-

nosis. Consult the haematologist immediately before undertaking any laboratory investigations; bleeding and clotting times are quite unsatisfactory, and special investigations may well be required, such as factor VIII clotting activity or related antigen assay.

Endocrine disorders

Adrenocortical function testing

- Blood pressure: is low in hypoadrenocorticism, high in hyperadrenocorticism.
- Plasma cortisol levels: the diurnal rhythm of plasma cortisol is a sensitive index of adrenal function; plasma cortisol values are normally highest between 6.00 and 10.00 a.m. and lowest between midnight and 4.00 a.m. Samples taken at 8.00 a.m. and 4.00 p.m. should differ by at least 5 µg/100 ml. The sample taken at 8.0 a.m. should be 5–25 µg/100 ml. Plasma cortisol at 8.00 to 9.00 a.m. is often below 6 µg/100 ml in hypoadrenocorticism. Diurnal variation in cortisol is lost in hyperadrenocorticism.
- Synacthen test (ACTH stimulation test): this is performed in the following way. Take 5 ml blood at 8.0 to 9.0 a.m. for the plasma cortisol level; give 0.25 mg Synacthen subcutaneously or intramuscularly; after 30 minutes, take a further blood sample for the plasma cortisol level. Normally, Synacthen results in a rise in cortisol levels to over 18 µg/100 ml. This rise is lost in hypoadrenocorticism (at an earlier stage in disease than the low cortisol level is found).
- Abdominal radiography: this may show calcified adrenals if tuberculosis is the cause of hypoadrenocorticism.
- Serum autoantibodies: patients with Addison's disease may have various circulating autoantibodies.
- Electrolytes: plasma potassium is raised and sodium reduced in hypoadrenocorticism in patients with Addison's disease.

Diabetes

Diabetes is diagnosed by testing for raised blood glucose either in the laboratory or at home with a glucometer. Blood is collected for laboratory testing in a special fluoride-containing bottle. A random whole blood glucose above 11 mmol/l or fasting level over about 7 mmol/l usually establishes the diagnosis. (Plasma glucose levels are about 1 mmol/l higher.) Diabetes is often detected at routine urinalysis by detecting glycosuria (and ketonuria) but there are other causes of glycosuria and of ketonuria, and diabetics do not always have glycosuria. Glucose tolerance testing is indicated only if blood sugar values are borderline.

Glucose tolerance test

A widely accepted simplified glucose tolerance test is as follows: give the patient 75 g glucose orally; assay blood glucose levels 2 hours later; a level greater than 11.1 mmol/l is diagnostic of diabetes; a level less than 11.1 mmol/l excludes diabetes.

Diabetic control

Diabetic control is best by serial measurements of blood glucose levels throughout the day. Usually, this is carried out by patients testing their own blood at home with a glucometer. Glycosylated haemoglobin or fructosamine are usually monitored regularly to assess longer term control. Non-diabetics have up to 7% glycosylated haemoglobin: 7–9% represents good control, over 13% shows poor control in diabetes.

Previously patients tested their urine at home and recorded the degree of glycosuria with Clinitest tablets, Diastix or Diabus strips. However, glycosuria tested in this relatively crude way does not usually become detectable until the blood sugar level is about 10 mmol/l (which already represents a considerable degree of hyperglycaemia), and it is therefore important to assess the renal glucose threshold to ensure that the measurement of glycosuria is not misleading as to blood glucose levels. This can be roughly estimated by comparing simultaneous urine and blood sugar concentrations.

The degree of ketosis can be rapidly assessed with Acetest tablets. A small amount of ketonuria, as shown by this test, is usually of no importance, but a strongly positive test, especially if confirmed by a positive ferric chloride reaction (Gerhardt's test), indicates a serious degree of ketosis. Confirmation is obtained by finding a low serum bicarbonate concentration.

Hyperparathyroidism

Blood for calcium levels should be collected early in the morning from a fasting patient. A tourniquet should not be used (venous stasis and a fall in pH alter calcium levels). The blood collection should be done along with serum for albumin assay (albumin levels influence calcium levels). This assay may need repeating several times to exclude hyperparathyroidism.

Sexually transmitted diseases

HIV

Diagnosis of HIV disease is from other causes of glandular fever syndromes (Table 3.9) and includes:

- clinical features
- lymphopenia

- a severe T-helper lymphocyte defect (reduced CD4⁺ cells)
- HIV antibodies (serotyping after counselling)
- excluding other sexually transmitted diseases.

Syphilis

Dark field microscopy of a lesion may demonstrate *Treponema pallidum*. Oral lesions should be washed first with saline to remove oral commensal treponemes. Also:

- serology is indicated
- the venereal disease research laboratory (VDRL) test is the screening test used
- since the VDRL test is not specific and may lead to false-positive results, a more specific test, such as the fluorescent treponemal antibody (FTA)-Abs or IgM-FTA-Abs, must be used where the VDRL test proves positive
- always exclude other sexually transmitted diseases.

Gonorrhoea

Gonococcal pharyngitis may be seen, particularly in men who have sex with men. Take a direct smear for Gram-staining (Gram-negative diplococci) and also take a bacteriological swab from the area, for culture and sensitivities. Always exclude other sexually transmitted diseases.

Hepatitis viruses B and C

Hepatitis B virus (HBV) and hepatitis C virus (HCV) tests include tests for antigens, antibodies and sometimes DNA. Patients positive for hepatitis B surface antigen (HB_sAg) should be screened for HB_eAg (e antigen). About

Table 3.9 Causes of glandular fever syndromes

Causal agent	Investigations
Epstein-Barr virus (EBV)	Paul-Bunell test EBV antibodies
Cytomegalovirus (CMV)	CMV antibodies
<i>Toxoplasma gondii</i>	Sabin-Feldman dye test Specific IgM antibodies
Human immune deficiency viruses (HIV)	HIV antibody titres Lymphopenia T4 (CD4) cell numbers
Human herpes 6	HHV-6 antibody

one in five are HB_eAg positive and at high risk of infectivity. Those who have HB_eAg should later be screened again at 3 months, and again if still positive. Those positive at 9 months are 'chronic carriers'.

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Treatment

Our universal aim should be to treat every patient as we would wish our families, or indeed ourselves, to be treated.

C Noyek

General comments

Collaboration with medical attendants

Many of the conditions seen in oral medicine practice have systemic manifestations, or they may be seen in patients with medical problems. It is crucial therefore always to collaborate closely with the medical attendants in the care of the patient. A specialist opinion may also be called for.

Referral to a specialist

Referral may be indicated when the practitioner is faced with:

- a complicated or serious diagnosis (especially cancer, HIV infection, pemphigus)
- a doubtful diagnosis
- a patient who has extra-oral lesions or possible systemic disease
- a situation where investigations are required, but not possible or appropriate to carry out, in general practice
- a situation where therapy may not be straightforward and may require potent agents or agents not prescribable in general practice
- a situation where drug use needs to be monitored with laboratory or other testing (e.g. for liver functional disturbances)
- a patient who needs access to an informed opinion or care outside normal working hours.

Should referral be required, it should always be in writing, giving a concise background to the referral, including:

- referring clinician's name, address, telephone, facsimile and e-mail
- patient's surname
- patient's first name(s)
- patient's date of birth
- patient's full address and telephone, facsimile and e-mail where possible
- patient's medical practitioner's name, address and telephone, facsimile and e-mail
- urgency of referral
- reason for referral
- relevant history
- relevant findings
- provisional diagnosis
- relevant medical history
- treatment already offered
- any special needs.

Psychological and sociological aspects of treatment

Treatment is much more than the simple use of a drug or the performance of a procedure; the whole psychology of the patient is important. Remember always that patients know whether the clinician cares, well before they care whether the clinician knows all the answers.

Many oral medicine conditions are chronic and have no cure, and for a few disorders the prognosis is poor or, fortunately rarely, the condition may even be fatal. Therefore, compassion and patient education are important. Empowering patients allows them to take control of their lives and decisions affecting their well-being. Such education and reassurance is always helpful; a supportive and understanding clinician is invariably welcomed by the patient, their partner and their family.

It is important to:

- Do no harm
- Manage the patient as a whole, in the context of their individual perceptions, aspirations, general health and social setting.
- Offer hope. Not all conditions can be cured, but most can be controlled or at least ameliorated. General improvements in oral health also help control symptoms in several other oral disorders.
- Work with the patient and family, and involve the patient in all decisions. Discuss the condition, diagnosis and possible therapies with the patient (and possibly partner and family).
- Warn of possible consequences (good and bad) of treatment or of no treatment.

- Obtain express informed consent before any invasive procedure.
- Offer advice on what patients themselves can do for their problems, including support from family, partners, friends and other bodies (e.g. alcohol, smoking or other drug support groups), disease support groups (e.g. cancer help groups or the Sjögren's Syndrome Society) or other information sources (e.g. patient information sheets, the Internet).

Lifestyle changes

There is no doubt that lifestyle habits such as the use of tobacco products, areca nut products and alcoholic beverages should be discouraged, especially in patients with oral mucosal diseases. Indeed, sometimes, the cessation of these habits may lead to resolution of the lesion.

Symptomatic care

Specific therapies are not available for all conditions, and the best that can be offered is the control of symptoms; this is called symptomatic treatment. Local antiseptics (e.g. 0.2% aqueous chlorhexidine mouthwashes) may aid resolution of mucosal lesions. Attention should be directed to relieving the following:

- Pain and discomfort: antipyretics/analgesics, such as paracetamol/acetoaminophen, help relieve pain and a soft diet may help. Erosive or ulcerative lesions can be protected with Orabase or Zilactin. Topical agents such as 0.1% benzydamine mouth rinse or spray may help symptomatically (see Appendix 2).
- Fever: adequate fluid intake is important and antipyretics/analgesics such as paracetamol/acetoaminophen help relieve fever.
- Anxiety: patient information is an important aspect in management and goes a long way to relieve anxiety, but there may need to be recourse to mild anxiolytics such as diazepam 2.5 mg or temazepam 5 mg.

Oral hygiene

Dental staff should ensure the patient has appropriate oral health education, and maintains particularly good oral hygiene, since the limited evidence available suggests that good oral hygiene helps the resolution of some lesions as well as gingivitis.

The most important device in oral hygiene is a toothbrush; many are effective:

- soft toothbrushes and silica-based toothpastes are less abrasive
- electric toothbrushes may assist oral hygiene in those with impaired manual dexterity.

Toothpastes are available that offer tooth whitening, plaque control, desensitisation, tartar control and tooth remineralisation.

Antiplaque agents are commonly used, particularly if the patient is immunocompromised. Many mouthwashes have only a transient antiseptic activity.

- Chlorhexidine digluconate is the most widely used antiplaque agent. Active especially against Gram-negative rods, it helps control plaque and periodontal disease and has some anti-caries and anti-fungal activity. It has good substantivity (ability to bind to hard and soft tissues and be released over a long period), but binds tannins and thus can cause dental staining if the patient drinks coffee, tea or red wine. Rarely, it causes other adverse effects, including:
 - overgrowth of enterobacteria (e.g. in leukaemic patients)
 - mucosal desquamation
 - hypersensitivity
 - salivary gland pain or swelling.
- Triclosan is a chlorinated bisphenol with substantivity and a broad spectrum of antibacterial activity, and a significant anti-plaque effect, without staining the teeth.
- Phenolics such as Listerine have some anti-plaque effect and do not stain teeth, but have low substantivity.
- Oxygenating mouthwashes may have a place in the control of anaerobic infections, such as necrotising gingivitis.
- Sanguinarine is a natural product with activity against bacterial plaque; it has been incriminated in some oral white lesions.

Fluoride mouthwashes are helpful for anticariogenic activity, especially useful for patients with dry mouth.

Diet

A healthy balanced diet is indicated to help resolution of mucosal lesions. In particular:

- Many mucosal lesions are aggravated by irritants such as tobacco and alcohol, and these also decrease salivary flow and should thus be avoided.
- A softish diet, avoiding toast and potato crisps, spices and acids such as in tomatoes and citrus fruits, may be indicated for a short period whilst a patient has a sore mouth.
- A softish diet containing pureed non-irritant foods and cool moist fruits such as melon are helpful in persons with dry mouth or soreness.
- Although vitamin and iron deficiencies are not common, supplements may be required if the diet is lacking.

- Dietary control and fluoride use is essential in xerostomia, to avoid caries. Fluorides may be usefully applied in the dental office, and daily at home (1% sodium fluoride gels or 0.4% stannous fluoride gels). Young children may need fluoride supplements.

Surgery

This can range from the simple excision of a lump such as a papilloma, to removal of a tooth, or to resection of a malignant neoplasm. Referral to a surgeon may be indicated.

- All surgery is invasive.
- Only an operator adequately skilled in a procedure should perform it.

Other less-invasive or non-invasive treatments

These include:

- cryotherapy
- soft laser therapy
- photodynamic therapy
- appliances (e.g. splints, tissue conditioning).

Follow-up of patients

Though it is desirable to offer treatment for oral lesions, this is not always possible or indicated, and sometimes watchful waiting is required, by following up the patient. Sometimes, for example in suspected traumatic ulceration, the diagnosis can only be decided by removing predisposing factors, and then checking progress in 2 weeks to see if the lesion is healing.

Drug treatment

Always remember the following:

- Use the safest drugs; virtually all drugs can have some adverse effects. Use only drugs with which you are totally familiar and use their generic (non-proprietary) drug names.
- Check that the prescription is legible and that there is no history of allergy or untoward effect. Always check drug doses, contra-indications, interactions and adverse reactions.
- Warn the patient of possible adverse effects.
- Reduce drug doses when prescribing for children, the elderly and patients suffering from liver disease and kidney disease.

- Consider the possibility of altered drug metabolism. The cytochrome P450 system of enzymes in the gastrointestinal mucosa and liver metabolises many drugs, and various P450 isoenzymes (CYP isoenzymes) metabolise a discrete range of drugs by oxidation, typically reducing their effect. CYP isoenzymes may have different activities between individuals and ethnic groups; this increases, for example, the activity of some anxiolytics such as diazepam (up to 6% of whites but up to 23% of Asians are sensitive to diazepam). Antidepressants and analgesics may also be affected.

Some drugs, for example erythromycin, inhibit CYP leading to the reduced ability to metabolise drugs such as ciclosporin.

Grapefruit juice contains flavonoids that can inhibit CYP and thus increase the activity of, for example, ciclosporin and some protease inhibitors.

Some over-the-counter herbal preparations, such as St John's Wort, can induce CYP; they can thus reduce the effect of protease inhibitors, antidepressants, warfarin, anticonvulsants and the contraceptive pill.

Alcohol and smoking can affect CYP.

- Avoid drug use in pregnancy, where possible.
- Avoid giving aspirin to children under 16 years of age, because of the risk of Reye syndrome.
- Avoid aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) in patients with peptic ulcers, or bleeding tendencies such as haemophilia or thrombocytopenia and in those taking anticoagulant drugs, since they exacerbate bleeding.
- Avoid metronidazole, azoles and some other antimicrobials in patients on warfarin, since they displace it from plasma proteins and increase bleeding.
- Avoid tetracyclines in pregnancy or breast-feeding, as they cause tooth discoloration.
- Avoid intramuscular injections in patients with bleeding tendencies such as haemophilia or thrombocytopenia and in those taking anticoagulant drugs, as haematomas can result.

In the UK, the *British National Formulary (BNF)*, published by the British Medical Association and the Royal Pharmaceutical Society of Great Britain, which includes the *Dental Practitioners' Formulary (DPF)* is a valuable source of information and advice on therapy. The BNF is revised twice yearly, and only the current issue should be consulted; it is available on the internet. Hand-held devices, such as the Palm Pilot, have software such as *Epocrates*, which holds comprehensive drug data.

Prescribing for children

- Doses of all drugs are much lower for children than for adults; always check against the recommended dose per unit body weight (Table 4.1).
- Some drugs are contraindicated (e.g., tetracyclines are contraindicated under the age of 7–8 years, also, aspirin is contraindicated in all children under 16 years old).
- Some drugs (e.g. diazepam) are best avoided as they may have anomalous effects.
- Oral preparations are invariably preferable to injectable drugs.

Prescribing in pregnancy and during breast-feeding

Because of the danger of damage to the foetus, all drugs should be avoided in pregnancy, unless their use is essential. In particular avoid tetracyclines, which stain teeth, and retinoids and thalidomide, which are teratogenic.

Prescribing for the elderly

- Lower drug doses are almost invariably indicated.
- Compliance may be poor.
- Care should be taken when there is the possibility of renal or hepatic dysfunction; this will necessitate reduced doses.

Drugs and food absorption

Most oral drugs are best given with or after food. Oral drugs that should be given at least 30 minutes *before* food, since their absorption is otherwise delayed, include:

- aspirin
- erythromycin
- paracetamol/acetoaminophen
- penicillins (including ampicillin and amoxicillin)
- rifampicin
- tetracyclines (except doxycycline).

Table 4.1 Rough guide for prescribing for children

Age of child (years)	Percentage of adult drug dose
1	25
6	50
12	75

Grapefruit juice disturbs the absorption and metabolism of some drugs and therefore should be avoided by persons taking:

- ciclosporin,
- calcium channel blockers (e.g. nifedipine)
- terfenadine.

Adverse reactions to drugs

Almost any drug may produce unwanted or unexpected adverse reactions and some produce oral adverse reactions. No drug should be used unless there are good indications. The true incidence of adverse drug reactions is often not known, and many adverse reactions are probably not, at present, recognised as drug-related. A full medical history should always be taken and questions should be asked specifically about drug use (including over-the-counter preparations) and adverse drug reactions, since the medical status may influence the choice of drugs used. Polypharmacy should be avoided and practitioners should use only drugs with which they are familiar.

Patients should be warned if serious adverse reactions are liable to occur (e.g. systemic corticosteroids), and provided with the appropriate warning card to carry.

Patient information sheet

CORTICOSTEROID TREATMENT (this sheet is for systemic steroids only)

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- Corticosteroids are very helpful but must be used with caution.
- Always tell an attending doctor or dentist you are on steroids.
- Always carry your steroid card.
- The steroid dose must usually be increased if you are:
 - ill
 - have an accident
 - have an operation.
- Adverse effects seen on treatment for over 4 weeks can include:
 - weight gain and fat redistribution
 - hypertension (high blood pressure)
 - precipitation of diabetes
 - osteoporosis
 - mood changes
 - liability to fungal and viral infection.
- Alternate-day dosing reduces the adverse effects of steroids.

Subcutaneous injection of drugs

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This is used for injection of drugs such as:

- local anaesthesia
- epinephrine (adrenaline)
- insulin
- heparin
- opiate analgesics.

Subcutaneous injections can be given into a skin fold, pinched up over the anterior abdominal wall or anterior thigh, with vertical insertion of a 25G (orange hub) needle. After injections, there is a small chance that anaphylactic shock may occur.

Intramuscular injection

This is used to obtain a more rapid effect than a subcutaneous injection, or where intravenous injection is impractical or carries a greater risk of anaphylactic or cardiac stimulant reaction. A 23G (blue hub) needle is used. It is used for:

- epinephrine (adrenaline) in the emergency treatment of anaphylactic shock
- glucagon, in the emergency treatment of hypoglycaemia
- antipsychotics (e.g. chlorpromazine, haloperidol) in the emergency treatment of acute psychoses
- antimicrobials.

Adverse effects of intramuscular injections include:

- Pain.
- Bruising, due to local haematoma formation. Intramuscular injections are contraindicated in patients with bleeding tendencies (e.g. haemophilia or induced by anticoagulant therapy).
- Nerve damage, which may lead to paralysis, especially in bleeding disorders. This risk is minimised by using either the side of the thigh, or the upper, outer quadrant of the gluteus maximus muscle in the buttock or the deltoid muscle in the upper, outer arm.
- Collapse, usually due to a faint.
- Anaphylactic shock, especially after injections with antimicrobials such as penicillins.

Intravenous injection

This is used to achieve a rapid effect in emergencies, for example:

- epinephrine in the management of cardiac arrest only

- diazepam in the management of status epilepticus
- heparin in the management of acute pulmonary embolism.

Intravenous infusion through an indwelling catheter is used:

- when administration by other routes is not possible (e.g. blood transfusion, or fresh frozen plasma or coagulation factor concentrates)
- for hydration with intravenous fluids (e.g. saline or dextrose) when oral intake of fluids is not possible (e.g. unconsciousness or semiconsciousness, impaired swallowing (e.g. after stroke), vomiting, or fasting prior to surgery or other procedures)
- for antimicrobial treatment of severe infections or infective endocarditis prophylaxis when using, for example, vancomycin.

Veins preferred for intravenous injections are those in the antecubital fossa, the preferred sites for infusions are the forearm or dorsal hand veins (which allow joint mobility). Note that:

- Following insertion of the needle (usually 21G (green hub) or 23G (blue hub)) or catheter, the fact that the needle is in a vein and not elsewhere should be confirmed by aspiration of blood and by the absence of local pain or swelling on injection or infusion of a small amount of the material to be administered.
- Intravenous catheters should be taped in place, and sterile precautions (and rotation of catheter sites) observed to minimize the risk of local thrombosis and sepsis.
- When prolonged intravenous access is required (e.g. in treatment of endocarditis or malnutrition), a central venous catheter can be inserted (under full sterile conditions) into the internal jugular or subclavian veins. Such Hickman lines (central catheters) are also useful in monitoring central venous pressure and intravenous fluid replacement in circulatory shock.
- After any injections, anaphylactic shock may occur, especially with antimicrobials such as penicillins. The patient should be observed for 30 minutes, with facilities for resuscitation available.

Analgesia

Specific treatments for several orofacial problems are few and far between, and often all that can be offered is compassion and an agent to reduce the inflammatory response, or relieve discomfort or pain. Pain is the most important symptom suggestive of oral disease, but absence of pain does not exclude disease. There is considerable individual variation in response to pain, and the threshold is lowered by tiredness and psychogenic and other factors. It is important, where possible, to:

- Identify and treat the cause of pain.
- Relieve factors which lower the pain threshold (fatigue, anxiety and depression).
- Topical analgesics and a variety of over-the-counter topical preparations are available to treat 'mouth ulcers', though few have been proved effective in controlled trials.
- Systemic analgesics can reduce pain, in some cases through an anti-inflammatory action, such as NSAIDs. Try simple oral analgesics initially, before embarking on more potent or injectable preparations or opioids; avoid polypharmacy (see Appendix 2). Paracetamol/acetoaminophen may be useful and in children can helpfully be given in sugar-free syrups.
- Antidepressants are widely used for the treatment of neuropathic pain. Tricyclics with balanced effects on serotonin and noradrenaline re-uptake (e.g. amitriptyline, nortriptyline) may be more effective than those acting mainly on noradrenaline uptake (e.g. maprotiline).
- Anticonvulsants are useful for painful neuralgic conditions, especially trigeminal neuralgia, in which carbamazepine is particularly effective.
- Membrane-stabilising drugs, such as lidocaine and mexiletine, can give short-term pain relief.
- Capsaicin is an alkaloid used topically which, by depleting the neurotransmitter substance P in sensory nerve endings, and by blocking conduction in type-C nociceptive fibres, can be helpful in postherpetic neuralgia and some other painful orofacial conditions.

Non-steroidal anti-inflammatory drugs

NSAIDs, including aspirin, are useful analgesics but can:

- Produce a bleeding tendency, by interfering with platelet activity via cyclo-oxygenase 1.
- Cause peptic ulceration especially in those over 75 years old or who have a history of peptic ulceration. Thus it is best to add a proton pump inhibitor such as misoprostol. Ibuprofen appears to be the conventional NSAID with the lowest risk of gastrointestinal adverse effects. Selective inhibitors of cyclo-oxygenase 2 (cox-2 inhibitors), such as celecoxib, have fewer gastrointestinal effects.
- Cause further deterioration of renal function, if this is already impaired.
- In the third trimester of pregnancy, cause premature closure of the ductus arteriosus.

Aspirin has been in use longer than most NSAIDs, and the efficacy and adverse effects are well recognised. Aspirin is useful but it can also:

- worsen asthma
- cause fluid retention

- cause nausea, diarrhoea or tinnitus
- increase methotrexate toxicity
- interfere with a number of drugs, including antihypertensives and diuretics
- cause allergies
- cause Reye syndrome – a serious liver disease, in children under the age of 16 years
- in mothers who are breast-feeding, pass in milk to child.

Paracetamol/acetaminophen

Paracetamol/acetaminophen is often more useful as an analgesic since it is not a NSAID, though it also produces some platelet dysfunction. Chronic pain requires regular analgesia (not just as 'required') and it is important not to overdose with paracetamol – which is hepatotoxic in high doses.

Opioids, narcotics and drug addiction

- Opioids are narcotics. They are Controlled Drugs and are all capable of causing addiction.
- Opioids are analgesics used for moderate to severe pain.
- Opioids may cause dependence, constipation, respiratory depression, nausea, drowsiness and urinary retention.
- Drug addiction (illegal drug use) is increasingly common, particularly in urban areas. Addicts in need of a 'fix' will often falsely complain of severe pain or injury. Disturbed behaviour in a drug addict may be caused by withdrawal symptoms and the patient may need compulsory detention. If an addict is admitted to the ward, contact a licensed psychiatrist for heroin or cocaine to be given for addicts. The most serious problems in the management of addicts include:
 - overdose
 - withdrawal effects
 - behavioural problems (including theft)
 - violence
 - hepatitis
 - HIV infection
 - other infections.

Immunosuppressive and immunomodulatory agents

- Topical corticosteroids are useful in the management of many oral ulcerative conditions where there is no systemic involvement, such as recurrent aphthous stomatitis and lichen planus (see Appendix 2).
- These steroids are used locally on a lesion as a spray, gel or cream, or as

a mouthwash if there are extensive lesions.

- Creams, gels and sprays are better than ointments, since the latter adhere poorly to the mucosa. However, creams can be bitter and gels can irritate.
- The steroid needs to be in contact with the mucosa for some minutes for it to have any significant effect; patients should therefore time its use for at least 3 minutes on each occasion.
- Patients should not eat or drink for 30 minutes after using the steroid, in order to prolong contact with the lesion.
- The steroid can usefully be applied in a plastic splint worn overnight for treatment of desquamative gingivitis.
- Adverse effects are important mainly with systemic steroids. With many topical steroids there is little systemic absorption and thus no significant adrenocortical suppression. In patients using potent steroids for more than a month it is prudent to add an antifungal, since candidiasis may arise.

Other topical immunomodulatory agents

Topical immunosuppressants such as ciclosporin or tacrolimus can be:

- effective in ulcerative disorders
- more effective if used along with topical corticosteroids
- expensive
- only rarely, associated with adverse effects.

Intralesional corticosteroids

Intralesional corticosteroids are occasionally useful in the management of intractable local lesions, such as erosive lichen planus and orofacial granulomatosis (see Appendix 2). Intra-articular corticosteroids are occasionally indicated where there is intractable pain from a non-infective arthropathy. Some examples include:

- prednisolone sodium phosphate, up to 22 mg
- methylprednisolone acetate, 4–80 mg
- triamcinolone acetonide, 2–3 mg
- triamcinolone hexacetonide, up to 5 mg.

Systemic corticosteroids

Indications

Systemic corticosteroids are often indicated for the management of:

- pemphigus
- giant cell arteritis

- Bell's palsy
- multisystem diseases, such as lichen planus with oral, genital and cutaneous involvement
- severe or resistant oral ulceration in vesiculobullous conditions.

Adverse effects

Systemic corticosteroids must always be used with caution because of potential adverse effects, which may include:

- Adrenocortical suppression. This may occur after a course of more than 3 weeks of systemic steroids and may persist for 1 year or more. Adrenocortical suppression makes the patient liable to collapse if stressed, traumatised or having an infection, operation or general anaesthetic.
- Weight gain and mooning of the face. Weight should be monitored. A diet low in salt, fats and calories helps control weight and prevent hypertension.
- Hypertension: the blood pressure must always be monitored.
- Precipitation of diabetes: the blood glucose must always be monitored.
- Cataract: ophthalmological monitoring is indicated.
- Osteoporosis: patients on protracted courses should have bone densitometry monitoring and be given bisphosphonates and calcium.
- Avascular necrosis of the femoral head.
- Psychoses.
- Liability to infections, especially with viruses, fungi and mycobacteria such as tuberculosis.
- Predisposition to malignancy, such as lip carcinoma.

Alternate-day administration after breakfast reduces the adverse effects of steroids. Patients should always be given a steroid card, warned of possible adverse reactions, and warned of the need for an increase in the dose if ill or traumatised, or having an operation. A 'steroid sparing' effect can be achieved with drugs such as azathioprine (see Appendix 2), ciclosporin, colchicine, thalidomide, dapsone or pentoxifylline. However, these drugs may have other, sometimes, more serious, adverse effects, such as myelosuppression and liver damage.

Retinoids

Tretinoin as a 0.1% cream or 0.01% gel, or Acitretin (pro-drug of etretinate) 10–50 mg/day orally, may be of value in controlling lichen planus. Systemic retinoids are teratogenic and may disturb liver function and blood lipids.

Thalidomide

- Thalidomide was originally used in the 1950s as a sedative, but was withdrawn in 1961 because of birth defects when given to pregnant women.
- Since then it has been found to benefit several severe conditions unresponsive to other treatments, especially severe aphthae and Behçet's disease.
- Patients given thalidomide may need a pregnancy test to check this is negative before starting thalidomide treatment, must take effective contraceptive measures while taking thalidomide and for 3 months after finishing the tablets, and must not get pregnant.
- Nerve damage can occur during thalidomide treatment. Nerve conduction tests are needed before the start of treatment, and these should be repeated every 6 months.
- Nerve damage will recover on stopping the treatment in approximately 50% of cases, but in others may be permanent.
- Thalidomide makes most people feel drowsy. It should be taken at night.
- Drowsiness persisting during the day makes it unsafe for patients to drive or operate machinery, and may impair alertness and ability to think clearly. Alcohol must be avoided.

Antimicrobials

- The bacteria which cause most odontogenic infectious are sensitive to penicillins.
- Anaerobes have now been implicated in many odontogenic infections, and these often respond to penicillins or metronidazole.
- Amoxicillin 500 mg three times daily is effective, and produces high blood antimicrobial levels, with good patient compliance.
- Flucloxacillin 500 mg four times daily is also effective against many oral bacterial infections.
- If the patient is allergic, has had penicillin within the previous month (resistant bacteria) or has methicillin-resistant *Staphylococcus aureus* (MRSA) a different antimicrobial should be used.
- Drainage must be established if there is pus; antimicrobials will not remove pus.
- A sample of pus (as much as possible) should be sent for culture and sensitivities but, if antimicrobials are indicated, they should be started immediately and in adequate doses.
- If a lesion fails to respond to an antimicrobial reconsider possible:
 - Inadequacy of drainage.
 - Inappropriateness of the antimicrobial.
 - Inadequate antimicrobial dose.

Antimicrobial insensitivity of causal micro-organism. For example, staphylococci are now frequently resistant to penicillin and some show multiple resistances (e.g. MRSA) when vancomycin is usually effective.

Patient non-compliance.

Local factors (e.g. foreign body).

Unusual type of infection.

Impaired host defences (unusual and opportunistic infections are increasingly identified, particularly in the immunocompromised patient).

Non-infective cause for the condition.

In serious, unusual or unresponsive cases of infection, consult the clinical microbiologist.

Indications for the use of antibiotics

Infections (together with appropriate surgical or other measures) such as:

- cervical fascial space infections
- osteomyelitis
- odontogenic infections in ill or toxic patients (e.g. if the patient is immunocompromised)
- acute ulcerative gingivitis
- specific infections, such as tuberculosis and syphilis.

Antibiotics should be used in some instances of surgical conditions if they do not respond to local measures:

- pericoronitis
- dental abscess
- dry socket.

Antibiotics should be used for prophylaxis:

- of infective endocarditis in patients having invasive oral procedures
- in cerebrospinal rhinorrhoea
- in most facial or compound skull fractures
- in major oral, maxillofacial and craniofacial surgery (e.g. osteotomies or tumour resection)
- in surgery in immunocompromised or debilitated patients
- in surgery following radiotherapy to the jaws
- possibly in patients with hydrocephalus shunts having invasive oral procedures
- possibly in some patients with prosthetic joint replacements having invasive oral procedures, especially following rheumatoid arthritis.

Using antimicrobials

- The practitioner should attempt to obtain relevant specimens before commencing therapy.
- For most infections, a 5-day course of antibiotics is adequate.
- Antibiotic prescriptions should be reviewed at 48 hours and 5 days, and in the light of microbiology results.
- Most infections should be treated with a single antibiotic only. Exceptions include endocarditis prophylaxis, tuberculosis treatment and some infections in immunocompromised persons.
- Always enquire first about allergies.

Antifungals (see Appendix 2)

Antifungals are used:

- to treat oral or oropharyngeal fungal infections, but underlying predisposing factors should be corrected first
- until there is no evidence of residual clinical lesions or symptoms, and should be continued for at least 2 weeks more, to reduce the risk of recurrence
- topically often effectively and, importantly, they are without serious adverse effects apart from occasional drug interactions (e.g. topical miconazole can enhance the effect of warfarin)
- systemically and though sometimes more effective against *Candida*, can be associated with adverse effects or drug interactions.

Azoles may:

- Be hepatotoxic.
- Displace protein-bound drugs and thus enhance the activity of, for example, anticoagulants, producing a bleeding tendency.
- Interact with a number of drugs. An important interaction is to produce arrhythmias with terfenadine (and in the past with astemizole and cis-apride). They may also interfere with the oral contraceptive.
- Cause antifungal resistance (to ketoconazole, fluconazole, miconazole, itraconazole) and this is now becoming a significant problem in immunocompromised persons, especially those with a severe immune defect, who may show *Candida* species resistant to fluconazole and, sometimes, to other azoles.

Polyene antifungal agents

These are best and safely used topically for oral candidiasis in most instances, and include:

- Nystatin, which needs to be applied at least four times daily, 500,000

units for adults and 100,000 units for children. Higher doses may be required in immunocompromised patients. Compliance can be a problem because of the taste, but pastilles or suspensions often overcome this disadvantage. Nystatin, if swallowed, may lead occasionally to gastrointestinal side-effects such as nausea, vomiting and diarrhoea.

- Amphotericin, used as an oral suspension 100 mg/ml, or lozenges 10 mg, is an effective antifungal for oral candidiasis. It can be given intravenously for systemic candidiasis but there is then a considerable risk of toxicity, which may manifest as fever, vomiting, and renal, bone marrow, cardiovascular and neurological toxicity. The most significant toxicity when used systemically, is renal damage, which may develop in up to 80% of patients.
- Flucytosine (5-fluorocytosine) may be used as oral therapy for candidiasis in a dose of 50–150 mg/kg/day, in divided doses, four times daily. Toxicity is due to metabolic effects on bone marrow cells, nausea, vomiting and hepatic dysfunction. In addition, flucytosine is poorly tolerated in HIV/AIDS, with approximately half of patients developing leukopenia, and slightly less developing thrombocytopenia. *Candida albicans* strain B may be resistant.

Azole agents

These include imidazoles (clotrimazole, miconazole, econazole, ketoconazole) and triazoles (fluconazole and itraconazole). Azoles are synthetic antifungals with broad-spectrum activity and are fungistatic, but are expensive and usually used mainly systemically, though miconazole in particular is often used topically. Azoles inhibit the fungal cytochrome P450 dependent enzymes, which are essential catalysts for the 14-demethylation of lanosterol in sterol biosynthesis, and therefore block the synthesis of ergosterol, the principal sterol in fungal cell membranes. One adverse effect of azoles, therefore, is the accumulation of precursors of ergosterol. The imidazoles (ketoconazole and miconazole) have more effect on cytochromes than do the triazoles, and the latter thus tend to have less severe adverse effects. However, none of the azoles are entirely benign; hepatotoxicity may be common to all, and the potential for endocrine toxicities exists, particularly at high doses. Another effect is on the metabolism of other drugs such as ciclosporin, the dose of which should therefore be reduced, and there can be interactions with antacids, sucralfate, phenobarbitone, isoniazid, phenytoin, rifampicin, terfenadine, H₂ receptor antagonists and warfarin. Rifampicin, rifabutin and phenytoin can decrease antifungal levels.

Finally, resistance is increasingly reported. The development of cross-resistance of *C. albicans* to different azoles during treatment with a single azole derivative has been described.

Clotrimazole is used only topically as a 10 mg troche three times daily, because it has gastrointestinal and neurological toxicity. It is less effective than other azoles in patients with HIV infection.

Ketoconazole may be used topically as a cream to treat angular stomatitis. Ketoconazole is usually used systemically, 200–400 mg/day taken orally with food, since gastric acid is essential for its dissolution. Absorption can be enhanced by taking orange juice, carbonated beverages or glutamic acid. Ketoconazole is poorly absorbed from an empty stomach in HIV/AIDS because of gastric atrophy and reduced acid production, or if there is concurrent use of medications such as cimetidine, ranitidine and other antacids. It is also poorly absorbed if rifampicin or phenytoin are given. Adverse effects may include nausea, rashes, abdominal pain and pruritus, but especially liver damage. Transient disturbance of liver function (e.g. increased serum aminotransferase concentrations) is so common that regular monitoring with liver function tests is essential in all patients on systemic ketoconazole for more than a few days. Severe liver damage may sometimes occur. Ketoconazole also blocks hormone steroid synthesis and reduces testosterone levels. Adrenocortical suppression may also develop. Drug interactions with ketoconazole are summarised in Appendix 2, they include that with terfenadine to produce dysrhythmias, and it also increases the activity of anticoagulants, ciclosporin, midazolam and sulphonylureas. These adverse effects have restricted its use.

Miconazole is used mainly for topical treatment of various forms of candidiasis such as angular stomatitis. Miconazole lacquer is effective for the treatment of chronic atrophic candidiasis; chewing gum may be effective against intraoral candidiasis. Miconazole is also available for parenteral use against systemic mycoses, but the injection contains polyethoxylate castor oil which may provoke allergic reactions. Intravenous miconazole may also cause liver damage and pruritus, nausea, blood dyscrasias, hyponatraemia, hyperlipidaemia and dysrhythmias. Miconazole may interact with terfenadine to produce dysrhythmias, and it increases the activity of anticoagulants, ciclosporin, midazolam and sulphonylureas.

Fluconazole, like some other azoles, acts by inhibiting fungal ergosterol production, which is essential in cell wall formation, but it has little affinity for cytochromes, which is thought to explain its lower toxicity. Fluconazole is active against most *C. albicans*, though resistance may appear (see below) and it is less active against some non-*albicans* *Candida* species. It tends to be active against *C. parapsilosis* and *C. tropicalis*, but less active against *C. glabrata*, and is inactive against *C. krusei*. Fluconazole is well absorbed from the gut, even in the absence of gastric acidity, and absorption is rapid and nearly complete within 2 hours. Fluconazole appears to undergo relatively little metabolism in the body, elimination being predominantly renal with a half-life of approximately

30 hours, meaning that fluconazole can be given once daily, in a dose of 50–100 mg. It also enters saliva. Fluconazole has generally been well tolerated, toxicity is mild and infrequent and, with usual doses, fluconazole does not appear to suppress the synthesis of corticosteroid hormones. Nausea, headache and rashes may occur. Elevated plasma concentrations of tolbutamide, ciclosporin, phenytoin and warfarin have been observed after fluconazole administration. Drug interactions present less difficulties than those associated with ketoconazole (see Appendix 2), though it may interact with terfenadine to produce dysrhythmias, and increase the activity of anticoagulants, ciclosporin, midazolam and sulphonylureas. An oral suspension of fluconazole is also available.

Itraconazole is an orally active triazole which inhibits ergosterol biosynthesis in the fungal cell. It is available in 50 and 100 mg capsules and as a 10 mg/ml oral solution. Itraconazole has been successful at a dose of 200 mg daily for 4 weeks in the treatment of candidiasis. It has a long half-life and fewer side-effects than ketoconazole, but is expensive, is eliminated hepatically and its use is contraindicated in liver disease. Itraconazole is well absorbed, but absorption is impaired when gastric acid is reduced or when anatacids, rifampicin or phenytoin are given. Itraconazole may interact with terfenadine to produce dysrhythmias, and increase the activity of anticoagulants, ciclosporin, midazolam and sulphonylureas. Adverse effects of itraconazole have included altered liver function (but hepatotoxicity is less than that of ketoconazole) and hypokalaemia with hypertension due to accumulation of steroids with an aldosterone-like activity, mild leukopenia, nausea, epigastric pain, headache and oedema.

Voriconazole

Voriconazole is a relatively new triazole antifungal agent, mainly indicated for the primary treatment of acute invasive aspergillosis. The primary mode of action is the inhibition of fungal cytochrome-P450-mediated 14- α -lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. Elevated liver function tests, rash and visual disturbances are the main treatment-related adverse events.

Antiviral therapy

- Most acute viral infections resolve naturally, though in immunocompromised persons they may be severe, widespread or persistent.
- Immunocompromised patients with viral infections may thus well benefit from active antiviral therapy.
- Most antivirals achieve maximum benefit if given early in the disease.
- Antiviral resistance is now becoming a significant problem to immunocompromised persons, especially those with a severe immune defect.

- Some antivirals active against herpesviruses and some active against retroviruses such as HIV are available, but there are few other antiviral agents of proven efficacy.

Antivirals active against herpesviruses

Nucleoside analogues

Nucleoside analogues compete with natural nucleosides to block virus DNA synthesis. They include:

- Aciclovir, a guanosine analogue selectively phosphorylated to active form by herpes virus thymidine kinases. Aciclovir has a proven efficacy in herpes simplex infections, including herpes labialis. It is not effective against cytomegalovirus (which has no such thymidine kinase).
- Valaciclovir is a pro-drug of aciclovir.
- Ganciclovir, a guanosine analogue, is active against cytomegalovirus, but is more toxic than aciclovir, can produce neutropenia, may have carcinogenic activity and, if given with zidovudine, can produce profound myelosuppression.
- Cidofovir is a DNA polymerase chain inhibitor, active against cytomegalovirus, but is nephrotoxic and may produce eye damage.
- Famciclovir, a guanosine analogue, is particularly useful against herpesvirus and varicella-zoster virus, but produces DNA mutations that may predispose to cancer of the breast or testis. Famciclovir is a pro-drug of penciclovir.
- Penciclovir is a relatively new synthetic acyclic guanine derivative which:
 - possesses the same antiviral spectrum as aciclovir
 - has a similar mechanism of action to that of aciclovir, in that it undergoes phosphorylation in response to HSV viral thymidine kinase and is then further phosphorylated by host cell enzymes into a triphosphate, which selectively inhibits HSV viral DNA replication
 - has considerably more bioavailability – up to 77% against the 10–20% for aciclovir
 - has a longer intracellular effect than aciclovir
 - is more effective clinically than aciclovir
 - is cheaper than aciclovir
 - as a 1% cream applied every 2 hours for 4 days is effective in treatment herpes labialis.

Other antimicrobial agents

Newer anti-herpes agents for herpes labialis include 10% docosanol cream. Inosine pranobex may also be used to treat herpes simplex virus (HSV) infections. Cidofovir and ganciclovir are active against cytomegalovirus (CMV). Foscarnet can be used for HSV or CMV infections.

Antiretroviral agents

Antiretroviral agents have been developed in the past decade, though all are liable to fairly severe adverse reactions and resistance.

Nucleoside reverse transcriptase inhibitors (NRTIs) block HIV reverse transcriptase activity by competing with natural substrates and being incorporated into viral DNA where they act as chain terminators in the synthesis of pro-viral nucleic acids. The NRTIs often produce adverse effects and, perhaps more significantly, resistance may arise. Among the common effects of many are haematological toxicity, neurological toxicity, including effects on memory, cognition, motor and peripheral nerve function, and enhanced risk of oral infection, ulcers and erythema multiforme. They include:

- zidovudine (ZDV) (azidothymidine, sometimes termed AZT), which can also produce hyperpigmentation
- didanosine (dideoxyinosine, DDI), which can also produce xerostomia
- dideoxycytidine (zalcitabine, DDC)
- lamivudine (3TC)
- stavudine (D4T)
- tenofovir
- abacovir.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) directly bind to HIV reverse transcriptase to inhibit it. NNRTIs suffer from similar disadvantages to NRTIs, especially rashes. Only efavirenz and nevirapine are licensed in the UK, but delavirdine is also licensed in the USA.

Protease inhibitors (PIs) competitively inhibit an HIV aspartyl protease without affecting the human enzyme, and they induce a profound and sustained fall in HIV viral load and restore T-cell counts. Drug-induced lipodystrophy may cause dyslipidaemia and facial lipoatrophy. Taste abnormalities are common and oral and perioral paraesthesia can be disturbing adverse effects. Indinavir, which has activity related to vitamin A analogues, can also produce cheilitis. PIs include:

- indinavir
- nelfinavir
- amprenavir
- ritonavir
- saquinavir
- lopinavir.

Highly active antiretroviral therapies (HAART) are combinations, involving a protease inhibitor and other antiretroviral drugs, which have reduced the incidence of opportunistic infections, extended life substantially and decreased the infective load of HIV and other viruses. Such has been the effect of HAART, that the orofacial disease caused by HIV/AIDS which was

reduced by combination therapy, has now been significantly reduced by HAART. Conversely, oral and perioral adverse effects can arise and may sometimes result in patient non-adherence to anti-HIV therapy.

CNS-active drugs

Hypnotics

- Pain, anxiety or depression may cause insomnia.
- In hospital, patients may temporarily need a hypnotic, but this should not be prescribed without forethought.
- Benzodiazepines such as temazepam 10 mg nocte are, in general, the preferred hypnotics, but are contraindicated in severe respiratory disorders and are also addictive.
- Barbiturates and glutethimide should not be used; both are dangerous in overdose and barbiturates are addictive.
- Hypnotics often potentiate alcohol and other CNS depressants, and may impair judgement and dexterity.
- Hypnotics may be contraindicated in the elderly and in those with liver or respiratory disease.

Anxiolytics

- Identify and treat the cause of the patient's anxiety wherever possible.
- It is important to differentiate between agitated depression and simple anxiety; the treatment is different.
- Reassurance is often remarkably effective at calming the anxious patient but there are times when a mild anxiolytic such as diazepam 1–10 mg orally three times daily can be helpful (see Appendix 2).
- Numerous benzodiazepines are now available as anxiolytics. All may produce dependence (especially lorazepam) and there is often little to choose in terms of anxiolytic effect between the different drugs.
- Most benzodiazepines cause unsteadiness and some confusion.
- Beta blockers (e.g. propranolol) may be more useful if anxiety is causing tremor/palpitations.
- Drowsiness (particularly when used together with alcohol) and impaired judgement are common in patients taking anxiolytics, sedatives or tranquillisers. Patients should therefore be warned of the dangers of driving, operating machinery or making important decisions.
- Doses of anxiolytics should be reduced for the elderly, since side-effects, particularly sedation are common.

Tranquillisers

Phenothiazines are major tranquillisers and can cause extrapyramidal disorders, postural hypertension, confusion and hypothermia. Chlorpromazine

should be avoided in the elderly. These drugs should not be stopped suddenly after prolonged or high dosages have been used, as this may precipitate withdrawal symptoms or acute psychosis.

Antidepressants

Psychotherapy, drugs and possibly physical treatment are used for the treatment of depression. If there is any possibility of a suicide attempt the patient must be seen by a psychiatrist as a matter of urgency.

Antidepressants can be useful for the relief of some neuropathic pain, when they can have analgesic effect within 1–7 days (before they have any antidepressant effect) and at lower doses than needed for treatment of depression. Antidepressants:

- Must be prescribed only in limited amounts, as there is a danger that the patient may use them in a suicide attempt.
- May take up to 2–4 weeks before the antidepressant action takes place. Doses should be reduced for the elderly patient. Monitoring of plasma concentrations of the drug may be helpful in ensuring optimal dosage.
- Levels monitored in plasma can be helpful in ensuring optimal dosage.
- Should not be withdrawn prematurely. The natural history of depression is of remission after 3–12 months.
- Are usually contraindicated in patients with cardiac or liver disease.
- Doses should be reduced for the elderly patient.
- May have adverse effects. Antidepressants often have anticholinergic activity and thus adverse effects include:
 - dry mouth, but the complaint of dry mouth may also be a manifestation of depression
 - epileptogenic effects (tricyclics and fluoxetine)
 - drowsiness
 - visual impairment
 - constipation and urinary retention.
- Make it impossible for patients taking them to drive vehicles, as they may suffer drowsiness and visual impairment.
- May interact with other drugs as follows:
 - tricyclic antidepressants interact with norepinephrine (noradrenaline)
 - tricyclic antidepressants do not interact significantly with the epinephrine (adrenaline) in dental local anaesthetic solutions.
 - monoamine oxidase inhibitors (MAOIs) do not significantly interact with adrenaline in dental local anaesthetic solutions
 - other antidepressant interactions include those with alcohol, antiarrhythmics, antiepileptics, antihistamines, antihypertensives, antipsychotics, apraclonidine, beta blockers, brimonidine, diuretics, the contraceptive pill, nefopam and tramadol.

Anticonvulsants

Anticonvulsants are used for the treatment of idiopathic trigeminal neuralgia, once organic causes have been excluded. Carbamazepine is the standard treatment, but phenytoin may also be required if the pain is not controlled. As either may cause blood dyscrasias or hepatic dysfunction, it may be helpful to monitor full blood counts and liver function (see Ch. 36).

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SECTION II

PDFFREE COMUNIDAD ODONTOLOGICA

Common Complaints

5

PDFFREE COMUNIDAD ODONTOLÓGICA

Cervical Lymphadenopathy

KEY POINTS

Main causes of cervical lymph node enlargement

- **Infections:**
 - oral or local in the drainage area
 - upper respiratory tract
 - systemic
- **Malignant disease:**
 - oral or in the drainage area
 - upper respiratory tract
 - lymphoreticular
- **Others**

Neck lumps

The tonsil is lymphoid tissue and there is similar material in the posterior aspect of the tongue and the posterior wall of the pharynx. These three areas form a ring of lymphoid tissue around the oropharynx (Waldeyer's ring). Over a quarter of the lymph nodes in the body are connected with cervical lymph nodes situated in the head and the neck. It is not surprising then, that many diseases of the lymphoid tissue present primarily in this region.

A wide range of diseases may present with lesions in the neck (Fig. 5.1), but the most common complaint is of swelling and/or pain in the lymph nodes (Table 5.1). The dental surgeon can often detect serious disease through neck examination. Tenderness and swelling should be documented.

Lymph nodes that are tender may be inflammatory (lymphadenitis). Lymph nodes swollen from acute infections are usually tender, soft and discrete, while chronic infections give firm lymph nodes. Nodes that are increasing in size and are hard, or fixed to adjacent tissues may be malignant. Nodes that are enlarged and firm and matted or rubbery may be due to leukaemia. In the lymphomas particularly, the nodes may be rubbery, matted together



Figure 5.1 Visible swelling in the submandibular triangle of the neck

Table 5.1 More comprehensive table of causes of cervical lymph node enlargement

Infections
● Viral upper respiratory tract: an enlarged jugulodigastric (tonsillar) lymph node, is common
● Oral or local in the drainage area (dental, scalp, ear, nose or throat): including cat-scratch fever and staphylococcal and mycobacterial lymphadenitis
● Systemic: viral (e.g. infectious mononucleosis, cytomegalovirus, HIV infection) bacterial, including syphilis, tuberculosis, brucellosis fungal, including histoplasmosis parasitic, toxoplasmosis, leishmaniasis, tularaemia
Malignant disease
● Oral or in the drainage area (usually oral, scalp, ear, nose or throat; rarely thyroid)
● Lymphoreticular (leukaemia, lymphoma)
● Langerhans histiocytosis
Others
● Drugs (e.g. phenytoin)
● Mucocutaneous lymph node syndrome (Kawasaki disease)
● Connective tissue disease

and fixed to deeper structures. In the systemic infective disorders the nodes are usually firm, discrete, tender and mobile.

Both anterior and posterior cervical nodes should be examined as well as other nodes, liver and spleen if systemic disease is a possibility. Generalised lymphadenopathy with or without enlargement of other lymphoid tissue such as liver and spleen (hepatosplenomegaly) suggests a systemic cause.

The tonsillar ring should be examined.

Discrete swellings in the neck may occasionally be caused by disorders in:

- the salivary glands
- thyroid gland
- other structures.

More diffuse swelling of the neck may be caused by:

- infection
- oedema
- malignant infiltration
- surgical emphysema.

The location of a lump or swelling in the neck will often give a good indication of the tissue of origin, and the age of the patient may help suggest the most likely diagnoses (Table 5.2). The duration of the lesion is also

Table 5.2 Most common causes of swellings in the neck at different ages

Child (first decade)

- Lymphadenitis due to viral respiratory tract infection
- Kawasaki disease

Adolescent and teenager

- Lymphadenitis due to viral respiratory tract infection (second decade)
- Bacterial infection
- Glandular fever syndromes
- HIV infection
- Toxoplasmosis

Adult (third and fourth decades)

- Lymphadenitis
- Glandular fever syndromes
- HIV infection
- Malignancy

After fourth decade

- Lymphadenitis
- Malignancy

relevant: one that has been present since an early age is likely to be of congenital origin, while a lump appearing in later life and persisting may be malignant.

This chapter concentrates mainly on lymph node disease (Fig. 5.2).

Enlarged cervical lymph nodes

Lymph nodes can enlarge in a number of disorders (see Table 5.1), often because of disease in the local area of drainage, sometimes because of dis-

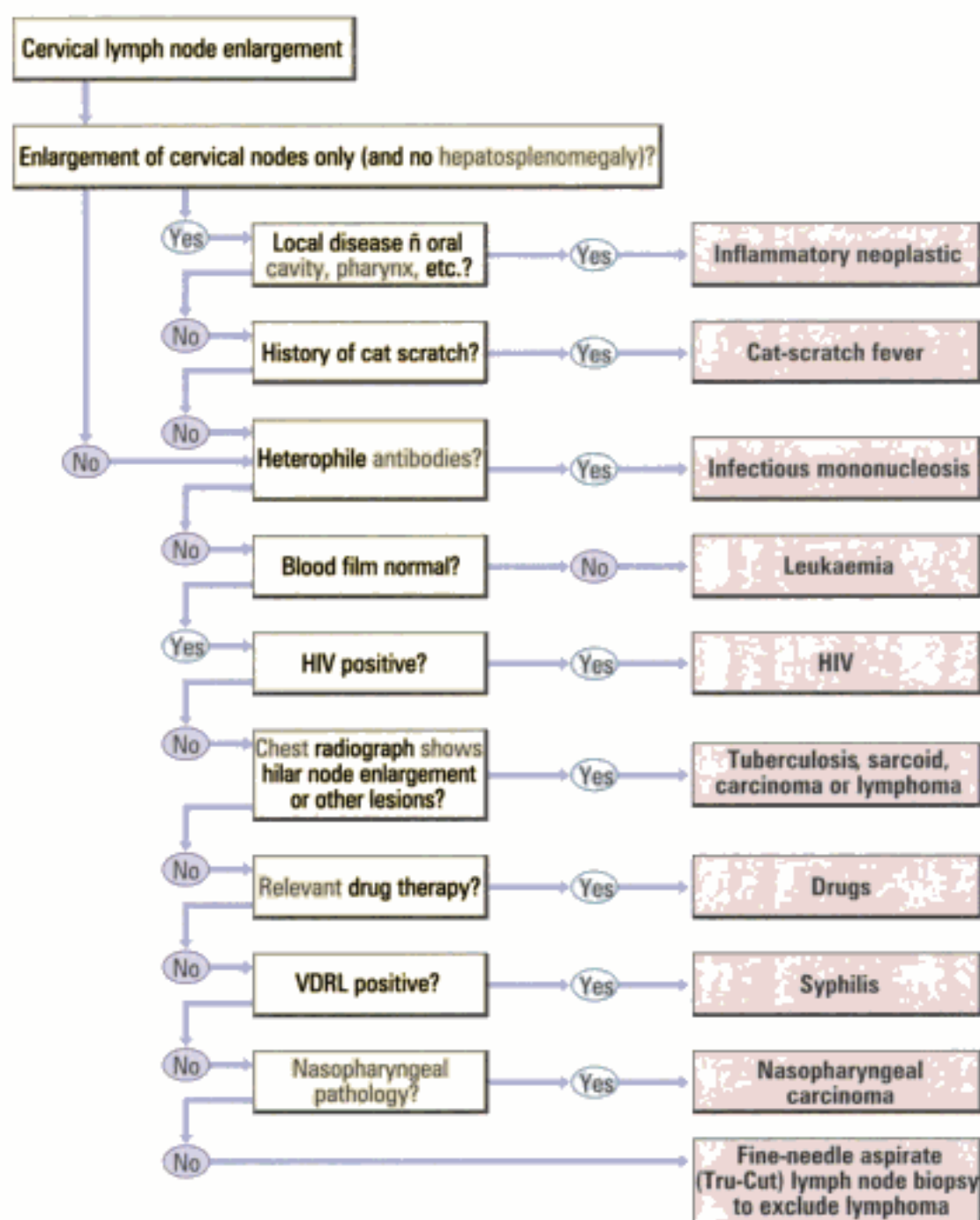


Figure 5.2 Management of cervical lymph node enlargement

ease affecting the wider lymphoreticular system (lymph nodes, liver and spleen). It is important therefore to consider the whole body when dealing with lymph node swellings; examination of other sites, particularly other nodes, liver and spleen may be necessary.

The main complaint with respect to cervical lymph nodes is usually of swelling. The patient may be aware that they have lymphadenopathy, usually termed 'glands in the neck'. Tenderness may have drawn the patient's attention to their presence. The history should include: date of onset of symptoms; details of any swelling, such as duration and character; and any details of pain experienced, such as duration, character, radiation, aggravating and relieving factors, and associated phenomena. Most disease is detected in nodes in the anterior triangle of the neck, which is bounded superiorly by the mandibular lower border, posteriorly and inferiorly by the sternomastoid muscle, and anteriorly by the midline of the neck. Nodes in this site drain most of the head and neck except the occiput and back of the neck. Lymphadenopathy in the anterior triangle of the neck alone is often due to local disease, especially if the nodes are enlarged on only one side. Lymph node enlargement can either be of the cervical lymph nodes alone or a generalised node enlargement.

Enlargement of the cervical lymph nodes alone usually arises because they are involved in an immune response to an infectious agent in the area of drainage and nodes are often firm, discrete and tender but are mobile (lymphadenitis). The focus of inflammation can usually be found in the drainage area, which is anywhere on the face, scalp and nasal cavity, sinuses, ears, pharynx and oral cavity. Such lymphadenitis only rarely leads to suppuration. The local cause may not always be found despite a careful search. For example, children (especially black children) occasionally develop a *Staphylococcus aureus* lymphadenitis or a similar problem due to atypical *Mycobacteria* (usually in a submandibular node) in the absence of any obvious portal of infection or any clear explanation for their susceptibility. Enlargement of cervical lymph nodes alone may occur when there is reactive hyperplasia to a malignant tumour in the drainage area, or metastatic infiltration. The latter may cause the node to feel distinctly hard, and it may become bound down to adjacent tissues ('fixed'), it may not be discrete, and may even, in advanced cases, ulcerate through the skin.

Generalised lymph node enlargement, including cervical nodes occurs in:

- Systemic infections, such as the glandular fever syndromes caused by Epstein-Barr virus, cytomegalovirus or toxoplasmosis, and HIV/AIDS. Lymphadenitis in tuberculosis may lead to neck swelling (scrofula) and suppuration (cold abscess).
- Idiopathic lesions such as sarcoidosis and mucocutaneous lymph node syndrome (Kawasaki disease), these are not known to be infective.

- Neoplasms of the lymphoreticular system, such as lymphomas and leukaemias (see Table 5.1), usually cause enlargement of many or all cervical lymph nodes and in some there is clinical involvement of the whole reticuloendothelial system, with generalised lymph node enlargement (detectable clinically in the neck, groin and axilla) and enlargement of both liver and spleen (hepatosplenomegaly).

Infective inflammatory conditions

Viral infections with predominantly upper respiratory and oral manifestations

- Usually several anterior triangle nodes – especially the jugulodigastric nodes – are enlarged, often bilaterally. Posterior triangle nodes are not enlarged and there is, of course, no generalised lymph node enlargement nor hepatosplenomegaly unless there are systemic complications or lesions elsewhere.
- Any viral upper respiratory infection from the common cold to viral tonsillitis can be responsible for enlarged cervical nodes (see Table 5.1).
- Oral viral infections that may cause cervical lymph node swelling are mainly those that also produce mouth ulcers such as:
 - herpes simplex stomatitis
 - herpangina
 - occasionally, herpes zoster of the trigeminal nerve (see Ch. 29).

Non-bacterial infections with multiple systemic manifestations

In these disorders there are usually several anterior and often posterior triangle nodes enlarged, with generalised enlargement and, in some instances, hepatosplenomegaly. Infections implicated are mainly:

- hand, foot and mouth disease (see Ch. 37)
- viral exanthemata (chickenpox, measles, rubella)
- glandular fever syndromes (Epstein-Barr virus, human herpesvirus 6 and cytomegalovirus infections and toxoplasmosis) and HIV/AIDS.

Acute non-specific bacterial infections

Most of these infections are non-specific. Usually only one or two nodes are enlarged, often unilaterally and only in the anterior triangle in most instances. However, lesions on the back of the scalp or neck may cause enlargement of posterior cervical nodes. Any bacterial infection in the area of drainage, such as a dental abscess, pericoronitis, sinusitis, or a boil in the nose, can cause enlargement of anterior cervical lymph nodes.

Acute specific bacterial infections

Occasionally, specific acute bacterial infections involve lymph nodes, particularly in young children who can develop acute lymphadenitis caused by *Staphylococcus aureus* in the absence of any detectable entry point for the organism. These infections, usually of a submandibular lymph node, should be treated with antibiotics – usually flucloxacillin because the *S. aureus* is often penicillinase-producing. If the lesion is fluctuant and pointing, surgical drainage is needed.

Chronic bacterial infections

- Generalised lymphadenopathy is a typical finding in secondary syphilis (see Ch. 37).
- Fine-needle aspiration (FNA) of the cervical lymph nodes is the most reliable diagnostic method for tuberculosis (see Ch. 37). Few patients have positive chest radiographs, there is a variable response to the tuberculin skin test, and often a negative culture for mycobacterial organisms.
- Atypical mycobacterial infections (see Ch. 37).
- Brucellosis.
- Cat-scratch disease (see Ch. 37).

Chronic granulomatous disease

Chronic granulomatous disease (CGD) is a rare genetic immune defect of leucocyte function in which neutrophils and macrophages fail to kill catalase-positive bacteria such as staphylococci. Patients suffer from recurrent pyogenic infections and may develop suppurating cervical lymph nodes showing granulomas on biopsy.

Parasitic: toxoplasmosis

For these conditions see Chapter 37.

Mucocutaneous lymph node syndrome (MLNS)

For MLNS (Kawasaki disease) see Chapter 37.

Non-infective inflammatory conditions

- Sarcoidosis (see Ch. 37).
- Crohn's disease (Ch. 37).
- Connective tissue diseases: cervical lymph nodes may be enlarged in rheumatoid arthritis or lupus erythematosus.
- Drug induced (e.g. phenytoin).

Neoplastic

PDFFREE.COM The neoplasms that usually metastasise to cervical lymph nodes are:

- Oral squamous carcinoma (see Ch. 20).
- Tonsillar cancer; clinically unsuspected tonsillar cancer is the commonest cause of metastasis in a cervical node of unidentified origin. Blind biopsy of the tonsil may reveal a hitherto unsuspected malignancy.
- Nasopharyngeal carcinoma; clinically unsuspected nasopharyngeal cancer is a common cause of metastasis in a cervical node of unidentified origin. Blind biopsy of the nasopharynx, particularly the fossa of Rosenmuller, may reveal a hitherto unsuspected malignancy.
- Thyroid tumours.

Usually one or more anterior cervical nodes are involved, often unilaterally in oral neoplasms anteriorly in the mouth, but otherwise not infrequently bilaterally.

Other metastatic neoplasms (other than lymphoid)

Rare causes of cervical metastases include metastases from the stomach or even testicular tumours to the lower cervical nodes, especially the supraclavicular nodes. In occasional patients with a malignant cervical lymph node, the primary tumour is never located.

Lymphoid malignancies

In lymphoid malignancies there is usually swelling both of anterior and posterior cervical lymph nodes together with generalised lymph node enlargement and often hepatosplenomegaly.

Langerhans histiocytosis

Management should be of the underlying condition (see Ch. 37).

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Dry Mouth (Xerostomia)

KEY POINTS

Main causes of complaint of dry mouth

- **Iatrogenic:**
 - drugs
 - irradiation
 - graft-versus-host disease
- **Disease affecting salivary glands**

Introduction

Saliva is essential to oral health, and patients who have decreased salivary flow (hyposalivation) suffer from lack of oral lubrication, affecting many functions, and may develop infections as a consequence of the reduced defences. Dry mouth (xerostomia) is a complaint that is the most common salivary problem and is the subjective sense of dryness which may be due to:

- reduced salivary flow (hyposalivation)
- changed salivary composition.

Advancing age is increasingly associated with dry mouth, but this is usually due to medication or disease, rather than age per se. Age does, however, result in an increase in adipose tissue and in a reduction of salivary acini, in salivary secretory reserve and in proteins such as MG1 and MG2 mucins.

Causes

Dry mouth is common in mouth-breathers and during periods of anxiety. Other than this, the main causes of dry mouth are iatrogenic.

- Drugs are the most common cause (Table 6.1). Drugs with anticholinergic or sympathomimetic or diuretic activity are responsible. These include:
 - atropine, atropinics and hyoscine
 - antidepressants, phenothiazines
 - antihistamines
 - antireflux agents such as proton-pump inhibitors (e.g. omeprazole)
 - opioids
 - diuretics
 - others (e.g. protease inhibitors or those used to treat urinary frequency).

There is usually a fairly close temporal relationship between starting the drug treatment or increasing the dose, and experiencing the dry mouth. However, the cause for which the drug is being taken may also be important. For example, patients with anxiety or depressive conditions may complain of dry mouth even in the absence of drug therapy (or evidence of reduced salivary flow).

- Irradiation for neoplastic conditions in the head and neck such as oral cancer, if it involves the salivary glands, can produce profound xerostomia.
- Chemotherapy.
- Graft-versus-host disease.
- Diseases of salivary glands can also cause of salivary dysfunction. These are mainly:
 - Sjögren syndrome (dry mouth and dry eyes)
 - sarcoidosis
 - HIV disease
 - hepatitis C virus infection
 - primary biliary cirrhosis
 - cystic fibrosis.
- Dehydration, as in diabetes mellitus, diabetes insipidus, hyperparathyroidism or any fever, is an occasional cause of xerostomia.
- Rare causes include salivary gland agenesis (aplasia).

Clinical features

The patient with hyposalivation may complain of dry mouth alone, or combined with other features such as dryness of the eyes and other mucosae

(nasal, laryngeal, genital), with other eye complaints (inability to cry, blurring, light intolerance, burning, itching or grittiness, and sometimes voice changes). There may also be systemic features (see Sjögren syndrome).

Table 6.1 More comprehensive list of causes of dry mouth

Iatrogenic causes: drugs

- Atropine, atropinics and hyoscine
- Antidepressants: tricyclic (e.g. amitriptyline, nortriptyline, clomipramine and dosulepin), selective serotonin re-uptake inhibitors (e.g. fluoxetine), lithium and some other antidepressants
- Antihypertensives: may also cause a compositional change in saliva. α_1 Antagonists (e.g. terazosin and prazosin) and α_2 agonists (e.g. clonidine) may reduce salivary flow. Beta blockers (e.g. atenolol, propranolol) reduce protein levels
- Phenothiazines
- Antihistamines
- Antireflux agents, such as proton-pump inhibitors (e.g. omeprazole)
- Opioids
- Cytotoxic drugs
- Retinoids
- Bupropion
- Others, such as:
 - Protease inhibitors
 - Didanosine
 - Diuretics
 - Ephedrine
 - Benzodiazepines
 - Interleukin-2

Other iatrogenic causes

- Irradiation
- Graft-versus-host disease

Disease

- Salivary gland disease:
 - Salivary aplasia (agenesis)
 - Sjögren syndrome
 - Sarcoidosis
 - Parotidectomy
 - Cystic fibrosis
 - Primary biliary cirrhosis
 - Infections (HIV, hepatitis C, human T lymphotropic virus 1 (HTLV-1))
- Other viruses
- Dehydration
- Psychogenic

There may be:

- difficulty in swallowing, especially in eating dry foods such as biscuits (the cracker sign)
- difficulty in controlling dentures in speech and swallowing
- difficulty in speaking, as the tongue tends to stick to the palate; this can lead to 'clicking' speech.
- mouth soreness
- unpleasant taste or loss of sense of taste
- a dry mucosa (Fig. 6.1) – the lips adhere one to another and an examining dental mirror may stick to the mucosa
- lipstick or food debris sticking to the teeth
- lack of the usual pooling of saliva in the floor of the mouth
- thin lines of frothy saliva may form along lines of contact of the oral soft tissues or in the vestibule
- saliva not expressible from the parotid duct
- a characteristic lobulated tongue, usually red, with partial or complete depapillation
- complications of xerostomia.

Oral complications

Oral complications of xerostomia may include:

- Dental caries, which tends to involve smooth surfaces and areas otherwise not very prone to caries – such as the lower incisor region. Caries can also involve roots and be severe and difficult to control.
- Candidiasis, which may cause:
 - burning sensation
 - taste changes
 - intolerance of acids and spices
 - mucosal erythema



Figure 6.1 Dryness evident on the tongue

lingual filiform papillae atrophy

angular stomatitis (angular cheilitis).

- Ascending (suppurative) sialadenitis, which presents with pain and swelling of a major salivary gland, and sometimes purulent discharge from the duct.

Diagnosis

Hyposalivation is a clinical diagnosis, made predominantly on the basis of the history and examination. The aims are to document the degree of salivary dysfunction and to determine the cause (Fig. 6.2).

Salivary function studies

It can be helpful to document salivary function not just from the history and examination findings but also by salivary function studies, which include studies of the salivary flow rates (sialometry), sialography, salivary scintiscanning and ultrasonography.

Salivary flow rates (sialometry)

Salivary flow rate estimation is a sensitive but non-specific indicator of salivary gland dysfunction usually carried out by one of two possible methods:

- Allowing the patient to dribble into a measuring container over 15 minutes. Such an unstimulated whole saliva flow rate exceeds 1.5 ml/15 min (0.1 ml/min) in a normal person.
- stimulated parotid saliva is collected after stimulation with, for example, 10% citric acid applied to the tongue. Saliva is collected in a Carlsson-Crittenden cup which covers Stensen's duct and is held in place by gentle suction, and in normal persons should exceed 1 ml/min.

Sialography

Sialography, in which radio-opaque dye, often iodine-based, is introduced into the salivary duct, is non-specific. It may be of value if there is dilatation or duct obstruction (e.g. by a calculus, though this rarely causes dryness), but carries risks of discomfort and infection.

Salivary scintiscanning

Salivary scintiscanning non-invasively examines all major salivary glands simultaneously, but is associated with a small radiation hazard since technetium-99m, a γ -emitting radionuclide is used. It is not always available and is expensive.

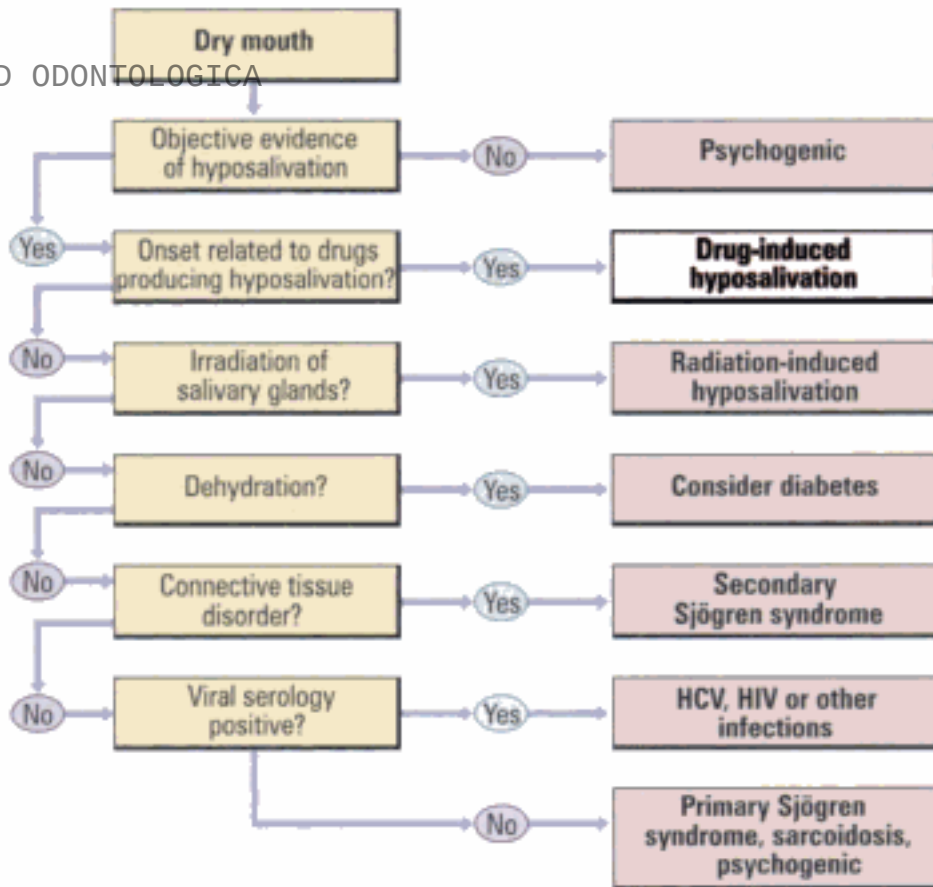


Figure 6.2 Algorithm for dry mouth (see Ch. 34)

Determination of the cause of xerostomia

The history and examination may help to determine the cause of dry mouth, but investigations may be indicated to exclude systemic disease, particularly to exclude:

- connective tissue disorders
- Sjögren syndrome
- sarcoidosis
- diabetes
- viral infections (hepatitis C; HIV; HTLV-1).

Commonly used investigations may thus need to include:

- Eye tests, using Schirmer and slit-lamp examination, mainly to exclude Sjögren's syndrome (see Ch. 34).
- Urinalysis, mainly to exclude diabetes.
- Blood tests:

erythrocyte sedimentation rate (ESR) or plasma viscosity – a non-specific test mainly to exclude Sjögren syndrome or sarcoidosis
antinuclear antibodies (ANA) – including SS-A and SS-B antibodies, mainly to exclude Sjögren syndrome and sarcoidosis (see Ch. 34)

rheumatoid factor (RF), mainly to exclude Sjögren syndrome
 serum immunoglobulin levels, a non-specific test mainly to exclude
 connective tissue diseases
 serum angiotensin-converting enzyme (SACE), mainly to exclude
 sarcoidosis
 serology, to exclude viral causes
 blood glucose.

- **Imaging:**
 - chest radiography, mainly to exclude sarcoidosis
 - ultrasonography, mainly to exclude Sjögren syndrome or neoplasia
 - magnetic resonance imaging (MRI), mainly to exclude Sjögren syndrome.
- Salivary biopsy may be indicated if there is suspicion of organic disease of the salivary glands. Although it is perfectly possible to biopsy the parotid or other major gland, there is a small risk of nerve damage or salivary fistula, and an extra-oral approach will leave a small scar. Therefore, biopsy of minor salivary glands is usually done. Glands in the lower labial mucosa are selected (labial salivary gland biopsy), since they are readily biopsied through a simple incision in the labial mucosa under local analgesia. The incision is paramedian, placed in the lower labial mucosa (avoiding any clinically obvious mucosal lesions which could confuse the diagnosis) and is thus not visible externally. Four to six lobules of salivary glands should be removed. The wound is closed with one or two sutures and, apart from mild discomfort in many and anaesthesia or hypoaesthesia in some cases, complications are rare.

It is important to recognise that some patients complaining of a dry mouth have no evidence of a reduced salivary flow or a salivary disorder. There may then be a psychogenic reason for the complaint.

Management

- Any underlying cause of xerostomia should, if possible, be rectified; for example, xerostomia-producing drugs may be changed for an alternative, and causes such as diabetes should be treated.
- Efforts should be made to avoid factors that may increase dryness, such as:
 - dry hot environments
 - dry foods such as biscuits
 - drugs (e.g. tricyclic antidepressants)
 - alcohol (including alcohol-based mouthwashes)
 - smoking.

- The mouth should be hydrated as regularly as possible. The lips may become dry, atrophic and susceptible to cracking and thus should be kept moist using a water-based lubricant or a lanolin-based product rather than one containing petroleum-derived lubricants (e.g. Vaseline). Olive oil, vitamin E or lip balm may help.

Salivary substitutes may help symptomatically. Various are available, including:

Water or ice chips: frequent sips of water are generally more effective than synthetic salivary substitutes.

Synthetic salivary substitutes, which vary in properties such as patient acceptability, fluoride content and pH (Table 6.2). Synthetic salivary substitutes usually contain: carboxymethylcellulose (UK: Glandosane, Luborant (contains fluoride), Salivace, Saliveze. USA:

Table 6.2 Some sialogogues and salivary replacements

Agent	Use	Comments
Sialogogues		
Pilocarpine (Salagen)	5 mg up to 3 times daily with food	Patient may be unable to see well enough to drive or operate machinery. Contraindicated in asthma, chronic obstructive air ways disease, glaucoma and pregnancy. Care with cardiac disease
Salivix	Malic acid	Pastille
Salivary replacements (artificial salivas)		
Glandosane	Sodium carboxy-methylcellulose base	Spray
Luborant	Sodium carboxy-methylcellulose base	Spray
Oralbalance	Lactoperoxidase, glucose oxidase and xylitol	Gel
Saliva Orthana	Mucin	Spray containing fluoride, or lozenge. May be unsuitable if there are religious objections to porcine mucin
Salivace	Sodium carboxy-methylcellulose base	Spray
Saliveze	Sodium carboxy-methylcellulose base	Spray

Patient information sheet**DRY MOUTH**

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- Saliva usually helps swallowing, talking and taste, and protects the mouth and teeth.
- Where saliva is reduced there is a risk of dental decay (caries), halitosis, altered taste sensation, mouth soreness and infections.
- Saliva may be reduced after radiotherapy or chemotherapy or the use of various drugs, after bone marrow transplants, in diabetes, in some viral infections, in anxiety/stress/depression, or in some salivary gland disorders.

Diagnosis

This is a clinical diagnosis mainly, but investigations may be indicated, including:

- blood tests
- eye tests
- urine analysis
- salivary flow rate tests
- salivary gland biopsy.

A simple biopsy, under local anaesthesia, of small glands inside the lower lip is quick and has few adverse effects except occasional minor anaesthesia.

- X-rays or scans.
- Chest x-ray.
- Sialography – your saliva is dyed and the amount measured.
- Scintiscanning – your saliva is radioactively marked and the amount measured.
- Ultrasound, like an x-ray but for the soft tissues.

10 steps to manage dry mouth

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- Sip on juices and other fluids throughout the day. Dryness can be combated by rinsing with water. Take small sips of fluids with each bite of food at meal times. Keep water at your bedside.
- Replace missing saliva with salivary substitutes (Artificial Saliva, Glandosane, Luborant, Oralbalance, Saliva Orthana, Salivace, Saliveze).
- Stimulate saliva with:
 - sugar-free chewing gums (EnDeKay or Orbit)
 - diabetic sweets
 - Salivix, if advised
 - drugs that stimulate salivation (Salagen) if advised by the specialist.

Contd

Patient information sheet – Contd

- Avoid spicy or dry foods or hard crunchy foods such as biscuits even when dunked in liquids. Take small bites and eat slowly. Eat soft, creamy foods (casseroles, soups), or cool foods with a high liquid content (melon, grapes, ice cream). Moisten foods with gravies, sauces, extra oil, margarine, salad dressings, sour cream, mayonnaise or yogurt. Pineapple has an enzyme that helps clean the mouth.
- Always take water or non-alcoholic drinks with meals.
- Avoid anything that may worsen dryness, such as:
 - drugs (e.g. antidepressants, unless they are necessary)
 - alcohol (including in mouthwashes)
 - smoking
 - caffeine (coffee, some soft drinks)
 - mouth-breathing.
- Protect against dental caries by avoiding sugary foods/drinks and by:
 - reducing sugar intake (avoid snacking and eating last thing at night)
 - avoiding sticky foods such as toffee
 - keeping your mouth very clean (twice daily toothbrushing and flossing)
 - using a fluoride toothpaste
 - using fluoride gels or mouthwashes daily before going to bed
 - having regular dental checks.
- Protect against thrush and halitosis by:
 - keeping your mouth very clean
 - keeping your mouth as moist as possible
 - rinsing twice daily with chlorhexidine (Chlorohex, Corsodyl, Eludril)
 - leaving dentures out at night
 - disinfecting dentures in hypochlorite (e.g. Milton, Dentural)
 - using antifungals if recommended by a specialist.
- Protect the lips with a lip salve.
- Consider a humidifier for the bedroom.

Moi-Stir, Orex, Salivart, Xero-Lube, Mouth-Kote), mucin (Saliva Orthana; also contains xylitol and fluoride) or glycerate polymer (Oral Balance; also contains xylitol, glucose oxidase and lactoperoxidase). A home preparation can be made using 1 teaspoon of glycerine in 8 ounces of water.

- Salivation may be promoted by using a stimulant:
 - chewing gums (containing sorbitol or xylitol, not sucrose)
 - diabetic sweets
 - cholinergic drugs that stimulate salivation (sialogogues), such as pilocarpine, bethanecol, cevimeline or anetholetrithione.

- Oral complications such as dental caries should be prevented and treated:

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Dietary control of sucrose intake is important.

Regular dental checks are required and monitoring of *Streptococcus mutans* counts may be helpful.

Topical fluorides reduce caries risk by reducing demineralisation and by increasing remineralisation.

Full-strength fluoride toothpastes containing 1000–1500 ppm fluoride should be used at least twice daily.

Fluoride rinses of 0.05% sodium fluoride should be used before retiring to bed at night.

Fluoride gel products provided in tightly adapted vacuform mouth guard carriers are also useful. Fluorides may be usefully applied in the dental office, and daily at home (sodium fluoride gels or 0.4% stannous fluoride gels).

Glass ionomer restorations can be useful since they release fluoride.

It is best to wait until a year of no new caries has elapsed before constructing new crowns.

- Oral complications such as candidiasis should be treated:

A rinse or swab from the oral mucosa should be taken to confirm the presence of candidiasis if there is soreness and signs of inflammation.

A commercial kit such as Ori-cult may be helpful.

Dentures should be left out of the mouth at night and stored in sodium hypochlorite solution, benzalkonium chloride or chlorhexidine.

Chlorhexidine, used in aqueous solution as a mouth rinse, has both antibacterial and antifungal effects, and there may be advantages to its use in dentate patients, due to some effect of chlorhexidine against cariogenic bacteria as well as *Candida*.

Antifungals should be used, until there is no evidence of mucosal erythema and symptoms and should be continued for at least 2 weeks more, to reduce the risk of recurrence. Topical antifungals tend to be most effective, since salivation is low and thus salivary antifungal delivery is not good. Topical antifungals are available as tablets which can be allowed to dissolve intra-orally, resulting in contact with mucosa while dissolving in the mouth. Unfortunately, the oral tablets typically are sugar-sweetened, yet it is important to avoid sucrose-sweetened products where natural teeth are present. It has become common practice to use the vaginal antifungal tablets intra-orally as these are not sucrose-sweetened. However, if the mouth is extremely dry, tablets may not dissolve, and in these cases liquid products are best. The polyenes, nystatin and amphotericin, which bind to membrane sterols in fungal cell membranes, damaging cell membranes and leading to death of the micro-organisms, are effec-

tive topically. Fluconazole systemically is also effective against oropharyngeal candidiasis. An antifungal such as miconazole gel or amphotericin or nystatin ointment should be spread on dentures or appliances before re-insertion.

- Oral complications such as bacterial sialadenitis should be treated: A swab should be collected of any pus expressed from the salivary duct, for bacterial culture and antibiotic sensitivities. Acute sialadenitis needs treating, usually with a penicillinase-resistant antibiotic such as flucloxacillin.

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Halitosis (Oral Malodour)

KEY POINTS

Main causes of halitosis

- Oral sepsis
- Dry mouth
- Starvation
- Smoking
- Some foods

- Drugs

- Systemic disease:
 - diabetes
 - respiratory
 - gastrointestinal
 - hepatic
 - renal
 - psychogenic

Introduction

Halitosis, from the Latin for breath *halitus*, is a fairly common complaint found mainly in adults. Halitosis is a problem analogous to body odour and is the cause for serious concern by many sufferers. Up to 30% of adults over 60 years old report either being conscious of their oral malodour, or having been told by others they have it. However, not all persons who believe they have halitosis actually have any malodour, and this can be a real clinical dilemma, and appears to have a psychogenic basis.

Oral malodour is common on awakening (*morning breath*) and is then usually a consequence of low salivary flow and oral cleansing during sleep. This rarely has any special significance, and can be readily rectified by eating, oral cleansing and rinsing the mouth with fresh water. Halitosis at other times is often the consequence of eating various foods such as garlic, onion or spices, or of habits such as smoking or drinking alcohol. The avoidance of these foods and habits is the best prevention.

Halitosis that is not due to these causes, is most often a consequence of oral bacterial activity, typically from anaerobes arising from:

- poor oral hygiene (Fig. 7.1)
- gingivitis (especially necrotising gingivitis)
- periodontal disease
- other types of oral sepsis
- infected extraction sockets
- residual blood postoperatively
- debris under bridges or appliances
- ulcers
- dry mouth.

The organisms implicated include:

- *Porphyromonas gingivalis*
- *Prevotella intermedia*
- *Fusobacterium nucleatum*
- *Bacteroides forsythus*
- *Treponema denticola*.

These anaerobes produce the chemicals that cause malodour in many instances, which include:

- volatile sulphur compounds (VSCs) (mainly methyl mercaptan, hydrogen sulphide and dimethyl sulphide)
- polyamines (putrescine and cadaverine)
- short-chain fatty acids (butyric, valeric and propionic acids).

The tongue is often also the location of many of the organisms implicated. Prevention of infective processes, improvement of oral hygiene, and sometimes the use of antimicrobial therapy can usually manage this type of halitosis.



Figure 7.1 Plaque accumulation and gingivitis

In the absence of oral infection, causes which may be responsible for oral malodour include:

- Starvation, probably partly due to oral stagnation.
- Drugs:
 - solvent abuse
 - chloral hydrate
 - nitrates
 - dimethyl sulphoxide
 - disulfiram
 - cytotoxic agents.
- Systemic disease. Medical help may be required to manage patients with a systemic background to their complaint:
 - In diabetic ketosis: the breath may smell of acetone.
 - Nasal sepsis or foreign bodies, or infection of the paranasal sinuses or respiratory tract may be a cause. In children, the insertion of foreign bodies such as small toys into the nose, and subsequent sepsis, is a common cause of halitosis. In adults, infections in the respiratory tract, such as tonsillitis, bronchitis, lung infections or tumours, may be responsible.
 - Gastrointestinal disease. Although *Helicobacter pylorii* has been suspected as a cause, it is an uncommon aetiology.
 - Hepatic failure.
 - Renal failure.
 - Psychogenic or psychosomatic factors may be causal. In some patients, no evidence of halitosis can be detected even with objective testing, and the halitosis may be attributed to a form of delusion or monosymptomatic hypochondriasis (self-halitosis, halitophobia). Such patients rarely wish to visit a psychological specialist because they fail to recognise their own psychological condition and never doubt they have oral malodour. Other people's behaviour, or perceived behaviour, such as apparently covering the nose or averting the face, is typically misinterpreted by these patients as an indication that their

Table 7.1 Causes of halitosis

- | | |
|---------------|--------------------------|
| ● Oral sepsis | ● Foreign body in nose |
| ● Dry mouth | ● Systemic disease: |
| ● Starvation | diabetic ketosis. |
| ● Smoking | respiratory disease |
| ● Some foods | gastrointestinal disease |
| | hepatic failure |
| | renal failure |
| ● Drugs | ● Psychogenic factors |

breath is indeed offensive. Such patients may have latent psychosomatic illness tendencies and may be mentally immature.

Many of these patients will adopt behaviour to minimise their perceived problem, such as covering the mouth when talking, avoiding or keeping a distance from other people, using chewing gum, mints, mouthwashes or sprays designed to reduce malodour, or excessively cleaning their tongue or mouth.

Diagnosis

Diagnosis (Fig. 7.2) is mainly clinical, made from:

- full history
- examination
- assessment of halitosis, usually by simply smelling the exhaled air (organoleptic method).

Some centres are able to also undertake objective measurements of the responsible:

- Volatile sulphur compounds, such as hydrogen sulphide and methyl mercaptan, using a halimeter (Interscan Corp., Chatsworth, CA, USA).

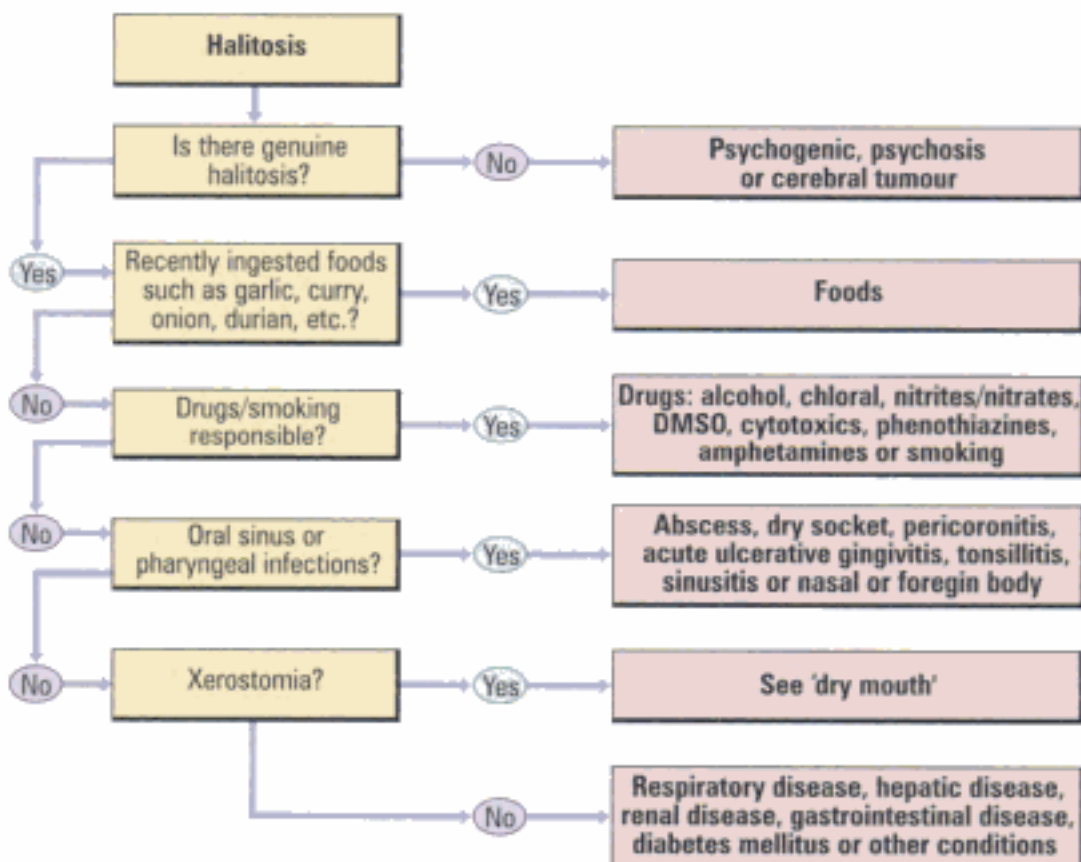


Figure 7.2 Algorithm for halitosis. (DMSO, dimethyl sulphoxide)

Other compounds however, are not detected.

- Oral flora, such as by the BANA (benzoyl-arginine-naphthyl-amide) test or dark field microscopy, which can be helpful, at least for patient education.

Patient information sheet

ORAL MALODOUR (halitosis)

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

Halitosis

- Is common on awakening.
- Is often far more obvious to the sufferer than others.
- If real is usually caused by diet, habits, dental plaque or oral disease.
- Can be measured with a halimeter.
- Often improves with oral hygiene.
- Can sometimes be caused by conditions of the sinuses, nose or throat.
- Is rarely caused by more serious disease.

10 steps to control breath odour

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- Treat any identifiable cause (this may need antimicrobials).
- Avoid odiferous foods such as onions, garlic and spices.
- Avoid habits that may worsen breath odour, such as:
 - alcohol
 - smoking.
- Take regular meals.
- Eat fresh fruit regularly: pineapple has an enzyme that helps clean the mouth.
- Brush your teeth after eating.
- Keep oral hygiene regular and good by:
 - prophylaxis
 - toothbrushing
 - flossing
 - rinsing twice daily with chlorhexidine (Chlorohex, Corsodyl, Eludril)
 - cetylpyridinium or other mouthwashes.
- Brush your tongue before going to bed: use a tongue scraper if that helps.
- Keep your mouth as moist as possible by using:
 - sugar-free chewing gums
 - diabetic sweets.
- Use proprietary 'fresh breath' preparations.
- If you have dentures, leave them out at night and in hypochlorite or chlorhexidine.

Management

The management of halitosis includes:

- Patient education.
- Treating the cause (medical assistance may be required).
- Avoiding smoking, foods such as onions, garlic and durian, and vegetables such as cabbage, cauliflower and radish.
- Regular meals and good oral hygiene, the latter involving dental prophylaxis, toothbrushing, flossing and tongue cleaning (with a scraper; this is best done before going to bed since scraping early during the day may induce retching).
- Oral antiseptics. These include products containing chlorhexidine (which is effective but may cause tooth-staining and occasional other adverse effects), cetylpyridinium, triclosan, essential oils or zinc chloride. All appear from published reports to be effective at reducing malodour, and most will reduce malodour for at least 3 hours, but some can be effective for much longer periods. Such products include a mouthwash which has two phases consisting of natural essential oils, triclosan and a water solution of cetylpyridinium chloride, plus sodium fluoride, and a toothpaste containing triclosan and a copolymer. In addition, chewing gum, parsley, mint, cloves or fennel seeds and the use of proprietary 'fresh breath' preparations may help.

Other products are available, such as those containing chlorine dioxide, and α -ionone, but the presented evidence for their efficacy is currently weak. Generally, it is recommended that mouthwashes should be used two or three times daily for at least 30 seconds. A multitude of these products is available over the counter, testimony to the extent of the perceived, or indeed real, problem of halitosis.

- In recalcitrant cases, the specialist empirically may use a 1-week course of metronidazole 200 mg three times daily in an effort to eliminate unidentified anaerobic infections.
- A number of 'fresh breath' clinics have been established, and may assist patients with the problem of halitosis.

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8

PDFFREE COMUNIDAD ODONTOLOGICA

Lumps and Swellings

KEY POINTS

Causes of oral lumps and swellings

- Normal anatomy
- Lesions:
 - developmental
 - inflammatory
 - traumatic
 - neoplasms
 - fibro-osseous lesions
 - hormonal
 - drug therapy
 - others

Introduction

Swelling and lumps in the mouth are common, and the tongue often detects even very small swellings or patients may notice a lump because it is sore. Some individuals discover and worry about normal anatomical features such as the parotid papilla, foliate papillae on the tongue, or the pterygoid hamulus. Most patients have only a passing interest in their mouths, but some examine their mouths out of idle curiosity, and some through fear (perhaps after hearing of someone with 'mouth cancer'). In contrast, many oral cancers are diagnosed far too late, often after being present several months, because the patient ignores the swelling. Some 'lumps' become ulcers, as in various bullous lesions and in malignant neoplasms. Many different conditions may present as oral lumps or swellings, causes including:

- The mouth's normal anatomy.
- **Developmental:** unerupted teeth, and tori are common causes of swellings related to the jaws.
- **Inflammatory:** dental abscess is one of the most common causes of oral swelling.
- **Neoplasms,** such as carcinoma, Kaposi sarcoma, salivary gland tumours and others, are important causes of oral swellings (Fig. 8.1). Occasionally metastatic malignant disease may present as a lump.
- **Traumatic:** haematoma may cause a swelling at the site. The flange of a denture impinging on the vestibular mucosa may stimulate a reactive irregular hyperplasia – the so-called denture granuloma or denture-induced hyperplasia.
- **Endocrine:** pregnancy may result in generalised gingival swelling (pregnancy gingivitis) or a discrete lump (pregnancy epulis). Diabetes predisposes to periodontal abscesses and occasionally giant cell lesions are seen in hyperparathyroidism.
- **Drug induced:** a range of drugs can produce gingival swelling – most common are phenytoin, ciclosporin and calcium channel blockers.
- **Viral lesions:** papillomas, common warts (verruca vulgaris), genital warts (condyloma acuminatum) and focal epithelial hyperplasia (Heck's disease) are all caused by papilloma viruses.
- **Fibro-osseous lesions:** fibrous dysplasia and Paget's disease can result in hard jaw swellings.

Diagnosis

- **Position:** the anatomical position should be defined as accurately as possible. The proximity of the lump to other structures (e.g. teeth, dentures) should be noted. Does the swelling have an orifice, or sinus? If



Figure 8.1 Salivary neoplasm causing palatal swelling

fluid is draining from the opening, is it clear, cloudy or purulent? Other similar or relevant changes elsewhere in the oral cavity should be noted (Table 8.1).

Midline lesions tend to be developmental in origin (e.g. torus palatinus; see Ch. 37).

Determine whether the lump is bilateral, since most neoplastic lumps are unilateral.

- Number of swellings, particularly with regard to whether the lesion is bilaterally symmetrical and thus possibly anatomical. Multiple lesions suggest an infective or occasionally developmental origin.
- Size: the size should always be measured and recorded. A diagram may be helpful. Thus, significant changes which may occur later can be recognised. In contrast, vague comments describing the swelling as 'medium' or 'large' are unhelpful.
- Shape: many swellings have characteristic shapes which point towards the diagnosis. Thus swelling of the parotid gland often fills in the space

Table 8.1 Lumps in the mouth by main location

Gingiva

- Chronic gingivitis
- Abscesses
- Hyperplastic gingivitis
- Fibrous epulis
- Giant cell tumour
- Exostoses
- Cysts
- Pyogenic granuloma
- Neoplasms
- Hereditary gingival fibromatosis
- Drugs:
 - phenytoin
 - ciclosporin
 - calcium channel blockers
- Pregnancy
- Sarcoidosis
- Crohn's disease
- Leukaemia
- Neoplasms
- Wegener's granulomatosis
- Amyloidosis
- Scurvy
- Midline lethal granuloma

Buccal

- Fibrous
- Mucocele
- Salivary neoplasm
- Carcinoma

Palate

- Torus palatinus
- Unerupted teeth
- Dental abscess
- Papilloma
- Neoplasms
- Carcinoma
- Lymphoma:
 - salivary gland neoplasm
 - Kaposi's sarcoma
- Others

Tongue

- Fibrous
- Papillitis
- Carcinoma
- Granular cell tumour

between the posterior border of the mandible and the mastoid process.

- **Colour and temperature:** brown or black pigmentation may be due to a variety of causes such as melanoma. Purple or red may be due to an angioma or Kaposi sarcoma. Is the lump pale in colour (suggesting underlying fibrosis, or soft tissues stretched over bony enlargement); red (suggesting inflammation); or deep red (suggesting haemangioma or giant-cell epulis)? Any variations in colour within the lump (e.g. a 'pointing' abscess) should be observed. The skin and mucosa overlying acute inflammatory lesions, such as an abscess, is frequently red and warm.
- **Tenderness:** inflammatory swellings such as an abscess are characteristically tender, although clearly palpation must be gentle to avoid excessive discomfort to the patient.
- **Discharge:** note any discharge from the lesion (clear fluid, pus, blood).
- **Movement:** the mobility of any swelling should be tested to determine if it is fixed to adjacent structures or the overlying skin/mucosa such as a neoplasm.
- **Consistency:** this may vary from soft and fluctuant to hard. Fluctuation refers to the presence of fluid within a swelling such as a cyst. This sign is elicited by detecting movement of fluid when the swelling is compressed. Palpation may then help assessment of its contents and these can be put into such categories as fluid (fluctuant because of cyst fluid, mucus, pus or blood), soft, firm, or hard like a carcinoma (indurated). Palpation may cause the release of fluid (e.g. pus from an abscess) or cause the lesion to blanch (vascular) or occasionally cause a blister to appear or expand (Nikolsky sign). Sometimes palpation causes the patient pain (suggesting an inflammatory lesion). The swelling overlying a bony cyst may crackle (like an egg-shell) when palpated. Palpation may disclose an underlying structure (e.g. the crown of a tooth under an eruption cyst) or show that the actual swelling is in deeper structures (e.g. submandibular calculus). Bimanual palpation should be used when investigating lesions in the floor of the mouth, cheek, and occasionally the tongue.
- **Surface texture:** the surface of a swelling may vary from a uniform smooth texture of many fibrous lumps to the grossly irregular. The surface characteristics should be noted: papillomas have an obvious anemone-like appearance; carcinomas and other malignant lesions tend to have a nodular surface and may ulcerate. Abnormal blood vessels suggest a neoplasm.
- **Ulceration:** some swellings may develop superficial ulceration, such as squamous cell carcinoma. The character of the edge of the ulcer and the appearance of the ulcer base should also be recorded. Ulcers should be examined for induration, which is indicative of malignancy.

Table 8.2 More comprehensive table of conditions which may present as lumps or swellings in the mouth

Normal	Cystic
● Pterygoid hamulus ● Parotid papillae ● Foliate papillae ● Unerupted teeth	● Eruption cysts ● Developmental cysts ● Cysts of infective origin
Developmental ● Haemangioma ● Lymphangioma ● Maxillary and mandibular tori ● Hereditary gingival fibromatosis ● von Recklinghausen's neurofibromatosis	Hormonal ● Pregnancy epulis/gingivitis ● Oral contraceptive (pill gingivitis)
Inflammatory ● Abscess ● Pyogenic granuloma ● Crohn's disease ● Sarcoidosis ● Wegener's granulomatosis ● Infections ● Insect bites ● Others	Drugs ● Phenytoin ● Ciclosporin ● Calcium channel blockers
Traumatic ● Haematoma ● Epulis ● Epithelial polyp ● Denture granulomas	Blood dyscrasias ● Leukaemia and lymphoma
	Benign neoplasms
	Malignant neoplasms
	Others ● Angioedema ● Amyloidosis ● Other deposits

- **Margin:** the margins of the swelling may be well defined or poorly defined. This may give some indication of the underlying pathology. Thus, ill-defined margins are frequently associated with malignancy, whereas clearly defined margins are suggestive of benign growth.
- **Associated swelling:** some conditions are associated with multiple swellings of a similar nature (e.g. neurofibromatosis).

The nature of many lumps cannot be established without further investigation.

- Any teeth adjacent to a lump involving the jaw should be tested for vitality, and any caries or suspect restorations investigated.
- The periodontal status of any involved teeth should also be determined.

- Imaging is required whenever lumps involve the jaws, and should show the full extent of the lesion and possibly other areas. Special radiographs (e.g. of the skull, sinuses, salivary gland function), computed tomography (CT scans), magnetic resonance imaging (MRI) or ultrasonography may, on occasions, be indicated. Photographs may be useful for future comparison.
- The medical history should be fully reviewed as systemic disorders may be associated with intra-oral or facial swellings (Table 8.2). Blood tests may be needed, particularly if there is suspicion that a blood dyscrasia or endocrinopathy may underlie the development of the lump.

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9

PDFFREE COMUNIDAD ODONTOLOGICA

Pain

KEY POINTS

Causes of orofacial pain

- Local disease, especially odontogenic pain
- Neurological
- Vascular
- Psychogenic
- Referred pain

Introduction

Pain in the teeth, mouth, face or head is the main reason why many patients consult their dental surgeon.

Significance

Most orofacial pain arises from diseases of the teeth (Fig. 9.1), but there can be a range of causes. Some headaches have an obvious but unimportant cause (e.g. hangovers), others have no obvious underlying pathology (e.g. postcoital headache), some can threaten sight (e.g. giant cell arteritis, benign intracranial hypertension) and others can be life-threatening (e.g. subarachnoid haemorrhage, bacterial meningitis, brain tumours).

Most acute pain has a simple cause and there are no serious sequelae but some, such as an acute ('thunderclap') headache or progressive subacute headache may have sinister implications such as an intracranial haemorrhage or meningitis and warrants urgent investigation.

Most recurrent headaches (tension-type, migraine and cluster headaches) or orofacial pain are not life-threatening, but they can interfere with the quality and enjoyment of life.

Causes

Mostly there is a local cause – usually the sequelae of dental caries (odontogenic pain), but a wide range of diseases apart from local disorders can cause orofacial pain, including neurological, vascular and psychogenic causes.

Diagnosis

The most important means of diagnosis of orofacial pain is the history. In order to differentiate the widely disparate causes, it is essential to determine key points about the pain (Table 9.1):

- Location: valuable information can be obtained by watching the patient when asked if the pain is localised or diffuse. For example, patients frequently point with one finger when describing trigeminal neuralgia, but atypical facial pain is much more diffuse and may radiate.
- Character: patients should be asked about the severity and whether the pain is 'sharp', 'dull', 'aching', 'throbbing' or 'shooting'. Ask the patient to rate the pain severity on a scale of zero (no pain) to 10 (most severe pain that the patient has experienced), or ask them to mark this on a line divided into 10 equal sections (visual analogue scale) or use an assessment instrument such as the McGill pain questionnaire. These help assess the severity, accepting always that it is subjective, and may also



Figure 9.1 Dental abscess; odontogenic causes are the main reasons for orofacial pain

Table 9.1 More comprehensive table of causes of orofacial pain**Local disorders**

- Teeth and supporting tissues
- Jaws
- Maxillary antrum
- Salivary glands
- Pharynx
- Eyes

Neurological disorders

- Idiopathic trigeminal neuralgia
- Malignant neoplasms involving the trigeminal nerve
- Glossopharyngeal neuralgia
- Herpes zoster (including postherpetic neuralgia)
- Multiple sclerosis
- SUNCT (severe unilateral neuralgia and conjunctival tearing) syndrome

Possible psychogenic causes

- Atypical facial pain
- Burning mouth syndrome
- Temporomandibular pain-dysfunction

Vascular disorders

- Migraine
- Migrainous neuralgia
- Giant cell arteritis
- Paroxysmal hemicrania
- Neuralgia-inducing cavitation osteonecrosis (NICO)

Referred pain

- Nasopharyngeal
- Ocular
- Aural
- Cardiorespiratory
- Angina
- Lesions in the neck or chest (including lung cancer)

be useful in monitoring the response to treatment. Disturbance of the normal sleep pattern by pain is also useful in assessing the severity.

- **Duration:** the average duration of each episode may help diagnosis. For example, pain from exposed dentine is fairly transient, lasting only for seconds, while the pain from pulpitis lasts for a longer period. Trigeminal neuralgia is a brief lancinating pain lasting up to about 5 seconds, migrainous neuralgia lasts 30–45 minutes, migraine lasts hours or days, while atypical facial pain is persistent.

- Frequency and periodicity: determine whether the pain occurs at specific times. A pain diary can help. For example, the pain of sinusitis is often aggravated by lying down, while periodic migrainous neuralgia frequently disturbs the patient's sleep at a specific time each night, around 2.00 a.m. The pain of temporomandibular joint pain-dysfunction syndrome may be more severe on waking.
- Precipitating, aggravating and relieving factors: ask if any factors influence the pain. For example, temperature often aggravates dental pain, touching a trigger zone may precipitate trigeminal neuralgia attacks, stress may worsen atypical facial pain, and alcohol may induce migrainous neuralgia episodes. It may be necessary to resort to leading questions, asking about the effects of temperature, biting, posture, analgesics, alcohol, etc.
- Associated features: some types of pain may be associated with other features which are helpful diagnostically. These include a swollen face in dental abscess, nausea and vomiting in migraine, or a history of nasal stuffiness or lacrimation in migrainous neuralgia.

Thus the answers to a series of features may be needed, including:

- Previous history.
- Character:
 - continuous
 - very severe
 - dull
 - throbbing
 - lancinating
 - burning sensation
 - interferes with sleep.
- Provoking or relieving factors:
 - worse with hot/cold
 - worse on biting
 - worse with exercise
 - worse on moving head
 - trigger point
 - other provoking factors known
 - stress related
 - alcohol changes pain.
- Other features:
 - ocular or nasal symptoms
 - neurological signs or symptoms
 - nausea/vomiting
 - relieved by analgesics/drugs
 - weight loss

temporomandibular click
trismus.

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Various instruments, such as IMPATH and the TMJ Scale are available to assess behavioural and psychological factors.

Local causes of orofacial pain

Most orofacial pain is related to dental disease – odontogenic causes.

Dentinal pain

Pain originating in dentine:

- Is sharp and deep.
- Is usually evoked by an external stimulus (normally food and drinks which are hot, cold, sweet, sour or, sometimes, salty). Although extreme changes in temperature (e.g. hot soup followed by ice-cream) may cause pain in intact, non-diseased teeth, pain evoked by natural stimuli usually indicates a hyperalgesic state of the tooth.
- Usually subsides within a few seconds of withdrawal of stimulus.
- May be poorly localised, often only to an approximate area within two to three teeth adjacent to the affected tooth. Sometimes, the patient is unable to distinguish whether the pain originates from the lower or the upper jaw. Pain from affected posterior teeth is more difficult to localise than that from anterior teeth. However, patients rarely make localisation errors across the midline.

Pulpal pain

Vitalometry using a pulp vitality tester may be indicated. Pain associated with pulp disease:

- Is spontaneous. Pain may be described by patients in different ways, and a continuous dull ache can periodically be exacerbated (by stimulation or spontaneously) for short (minutes) or long (hours) periods. The pain of pulpitis is frequently discontinuous and abates spontaneously; the precise explanation for such abatement is not clear.
- Is strong, and can be excruciating for many minutes.
- Is often throbbing.
- Is typically exacerbated by temperature change and pressure on a carious lesion.
- May increase and throb when the patient lies down, and in many

instances wakes the patient from sleep.

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● **Outlasts the stimulus** (unlike stimulus-induced dentinal pain).

- Is poorly localised, particularly when pain becomes more intense.
- Tends to radiate or refer to the ipsilateral ear, temple and cheek, but does not cross the midline.

Periodontal pain

Pain originating in the periodontium:

- is more readily localised than is pulpal pain
- may be less severe than pulpal pain
- is often associated with tenderness to pressure on the affected teeth
- is usually not aggravated by heat or cold.

Acute periapical periodontitis

Pain associated with acute periapical inflammation:

- Is spontaneous in onset.
- Is moderate to severe in intensity.
- Persists for long periods of time (hours).
- Is exacerbated by biting on the tooth and, in more advanced cases, even by closing the mouth and bringing the affected tooth gently into contact with the opposing teeth. In these cases, the tooth feels 'high' (extruded) and is very sensitive to touch.
- Has often been preceded by pulpal pain.
- Is usually better tolerated than the paroxysmal and excruciating pain of pulpitis.
- Is usually precisely localised and the patient is able to indicate the affected tooth. The improved ability to localise the source of pain may be attributed to the proprioceptive and mechanoreceptive sensibility of the periodontium that is lacking in the pulp. However, although localization of the affected tooth is often precise, in up to half of cases the pain is diffuse and radiates into the jaw on the affected side. During examination the affected tooth is located readily by means of tooth percussion.
- Is usually associated with a non-vital tooth.
- Is usually associated with tenderness to palpation in the periapical buccal vestibular area.
- May be associated with swelling of the face, caused by oedema and cellulitis or sometimes connected with fever and malaise. Usually, when the face swells, pain diminishes in intensity due to rupture of the pus through the periosteum of the bone around the affected tooth and the consequent decrease in pressure of the tooth apex.

Lateral periodontal abscess

- The pain is similar to that of acute periapical periodontitis, though often less severe, and is well localised and with swelling and redness of the gingiva.
- However, the swelling is usually located more gingivally than in the case of an acute periapical lesion.
- The affected tooth is sensitive to percussion and is often mobile and slightly extruded, and there is a deep periodontal pocket. Probing the pocket may cause pus exudation and subsequent relief from pain.
- The tooth pulp is usually vital.

Food impaction

The cause of food impaction is usually a faulty contact between the teeth because of caries or poor restorations. Examination shows a faulty contact between two teeth and often food trapped between these teeth; the gingival papilla is tender to touch and bleeds easily.

Food impaction interdentally can cause:

- localised pain that develops between or in two adjacent teeth after meals, especially when food is fibrous (e.g. meat)
- pain associated with a feeling of pressure and discomfort, which may gradually disappear until being evoked again at the next meal, or may be relieved immediately by removing the impacted food
- the adjacent teeth to be sensitive to percussion.

Cracked tooth

Examination may fail to elicit the cause of pain. Cracks may be revealed by biting on rubber, by fibre-optic illumination or by staining with, for example, disclosing solution. Teeth can crack under trauma and can give rise to pain which is:

- severe
- worse on biting
- often precipitated by hot or cold.

Pericoronitis

Acute pericoronal infections are common, and are related to incompletely erupted teeth partially covered by flaps of gingival tissue (operculum), particularly lower third molars. Pain is spontaneous and is often exacerbated by closing the mouth. In more severe cases, pain may be aggravated by swallowing, and there may be trismus and, occasionally, fever and malaise. Examination shows an operculum that is acutely inflamed, red and oede-

matous. Frequently, an opposing upper tooth indents or ulcerates the oedematous operculum.

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Acute necrotising gingivitis

Examination shows necrosis and ulceration of the marginal gingiva with different degrees of gingival papilla destruction. Similar features but with more intense pain may be seen in necrotising periodontitis in HIV/AIDS. Acute necrotising gingivitis may cause:

- Soreness and pain at the gingival margin. In the early stages some patients may complain of a feeling of tightness around the teeth. Pain is fairly well localised to the affected areas.
- Profuse gingival bleeding.
- Halitosis, usually.
- Metallic taste, sometimes.
- Fever and malaise, sometimes.

Mucosal pain

Pain from oral mucosal lesions can be either localised or diffuse. Localised pain is usually associated with an erosion or ulcer. Diffuse pain may be associated with a widespread infection, mucosal atrophy or erosion, a systemic underlying deficiency disease or other factors, and is usually described as 'soreness' or sometimes 'burning'. Mucosal pain may be aggravated mechanically by touch, or by sour, spicy, salty or hot foods.

Other local causes of orofacial pain

Jaws

Pain from the jaws can be caused by acute infection, malignancies, Paget's disease and direct trauma. Lesions such as cysts, retained roots and impacted teeth are usually painless unless associated with infection or fracture of the jaw. Odontogenic and other benign tumours of the bone do not normally produce pain, but malignant tumours usually produce deep, boring pain, sometimes associated with paraesthesia, hypoaesthesia or anaesthesia. Radiation therapy may result in severe pain due to infection and osteomyelitis associated with osteoradionecrosis.

Temporomandibular joint

Pain from the temporomandibular joint may result from dysfunction, acute inflammation, trauma, primary or secondary malignant tumours. Examination may reveal the masticatory muscles tender to palpation or occasionally the joint swollen and warm to touch or tender to palpation via the external auditory meatus. Pain from the temporomandibular joint:

- is usually dull
- is usually poorly localised
- may radiate widely
- is usually intensified by movement of the mandible
- may be associated with trismus because of the spasm in the masticatory muscles.

Salivary glands

Examination usually reveals the salivary gland swollen and sensitive to palpation. In acute parotitis, mouth-opening causes severe pain, and thus there is a degree of trismus. Salivary flow from the affected gland is usually reduced. Pain may be associated with fever and malaise. In children, the most common cause is mumps. In adults, pain from salivary glands results usually from blockage of a salivary duct by calculus or a mucus plug, or sialadenitis, when pus may exude from the duct orifice. Pain from salivary gland disorders:

- is localised to the affected gland
- may be quite severe
- may be intensified by increased salivation, such as before and with meals – the pain may wane in the minutes/hours following such salivary stimulation.

Sinuses and pharynx

Disease of the paranasal sinuses and nasopharynx can cause oral and/or facial pain. In acute sinusitis there has usually been a preceding cold followed by local pain and tenderness (but not swelling) and radio-opacity of the affected sinuses, sometimes with an obvious fluid level. Transillumination from a light in the oral cavity may show a fluid level. With maxillary sinusitis, pain may be felt in related upper molars and premolars, any of which may be tender to percussion. The pain of ethmoidal or sphenoidal sinusitis is deep in the nose. Pain in any type of acute sinusitis may be aggravated by a change of position of the head.

Tumours of the sinuses or nasopharynx can also cause facial pain. These tumours are often carcinomas which infiltrate various branches of the trigeminal nerve and can remain undetected until too late. Nasopharyngeal carcinoma often presents late, with facial pain, paraesthesia, ipsilateral deafness and/or cervical lymph node enlargement (Trotter syndrome).

Pressure on the mental nerve

Rarely, pain is caused by pressure from a denture on the nerve, which comes to lie on the crest of the ridge as the alveolar bone is resorbed in

the edentulous mandible. Either the denture should be relieved from the area or occasionally it is necessary to re-site the nerve surgically.

Neurological (neuropathic) causes of orofacial pain

Sensory innervation of the mouth, face and scalp depends on the trigeminal nerve, so that disease affecting this nerve can cause orofacial pain or indeed sensory loss – sometimes with serious implications.

Facial neuralgia caused by tumours or other lesions

Any lesion affecting the trigeminal nerve, whether it be traumatic, cerebrovascular disease, multiple sclerosis, infections such as HIV/AIDS, inflammatory or neoplastic (e.g. a nasopharyngeal or antral carcinoma), may cause pain, often with physical signs, such as facial sensory or motor impairment.

Idiopathic trigeminal neuralgia

Severe lancinating unilateral orofacial pain may be of idiopathic origin, and in the absence of identifiable organic cause is termed 'idiopathic trigeminal neuralgia' (see Ch. 36). Similar pain is experienced in the rare idiopathic short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing (abbreviated to SUNCT syndrome).

Other neuralgias

Glossopharyngeal and postherpetic neuralgias may also cause pain.

Vascular causes of orofacial pain

Several disorders in which the most obvious organic feature is vascular dilatation or constriction cause orofacial pain. The pain is usually obviously in the face or head rather than in the mouth, but occasionally can involve both, and can be difficult to differentiate from other causes of orofacial pain (Table 9.2). These include:

- migraine
- migrainous neuralgia
- giant cell arteritis.

A rare condition termed neuralgia-inducing cavitation osteonecrosis (abbreviated to NICO), related to disorders in blood coagulation, may also cause jaw pain.

Table 9.2 Differential diagnosis of orofacial pain

	Dental	Periodontal	Mucosal	Salivary glands	Neuralgic	Vascular	TMJ pain—dysfunction
Location	Mouth, ear, jaws, cheek	Tooth	Mucosa	Area of gland	Nerve distribution	Orbit or upper face	Temple, ear, jaw, teeth
	Poor, diffuse, radiating, does not cross midline	Good	Usually good	Usually good	Good	Usually good	Poor, but usually unilateral
Duration	Seconds to days	Hours to days	Hours to days	Hours to days	Seconds	Minutes to hours	Weeks to years
Character	Intermittent, sharp, paroxysmal	Steady, boring	Burning or sharp	Drawing, pulling	Lancinating, paroxysmal	Throbbing, deep	Dull, continuous
Precipitants	Hot and cold	Chewing	Sour and spicy foods	Eating	Touch, wind	Alcohol	Yawning, chewing
Associated features	Caries, exposed dentine	Advanced periodontitis	Abscess, erosions or ulcers	Salivary gland swelling	None usually	Lacrimation, injected eye, nasal discharge	Click in TMJ, trismus
Aetiology	Caries, trauma, gingival recession	Acute periodontitis	Varied	Saliva retention, infection	Idiopathic, multiple sclerosis	Vasomotor	Stress, parafunction
Treatment	Cracked tooth, restoration, endodontics	Endodontics or extraction	According to cause	Drainage, antibiotics	Carbamazepine, nerve block, cryoanalgesia neurosurgery	Triptans (clonidine, methysergide, lithium carbonate)	Antidepressants, other treatments

Other organic causes of headache or orofacial pain

Headache or orofacial pain is occasionally the presenting feature of:

- Exertion (including postcoital headache).
- Fevers.
- Hypertension.
- Meningeal irritation: severe headache with nausea, vomiting, neck pain or stiffness (with inability to kiss the knees) or pain on raising the straightened legs (Kernig sign) implies meningeal irritation. Urgent neurological attention is needed, since the pain may indicate meningitis, metastases or subarachnoid haemorrhage.
- Raised intracranial pressure: this is one of the most serious but also the least common causes of headache. The headache is severe, worse on waking and decreases during the day. It is aggravated by straining, coughing, sneezing or lying down. Nausea and vomiting are common. Neurological attention and examination for papilloedema is essential, since this may be caused by malignant hypertension, a tumour, abscess or haematoma. When no specific cause can be found it is termed 'idiopathic ('benign') intracranial hypertension', which may be precipitated by tetracyclines, vitamin A, nitrofurantoin and nalidixic acid and is associated with partial thrombosis of the superior sagittal sinus.
- Chronic obstructive airways disease.
- Some endocrinopathies, such as diabetes.
- HIV infection.
- Drug use (e.g. nitrites, phenothiazines).
- Paget's disease.

Chronic post-traumatic headache

Most persons who have had head injuries have local pain or tenderness at the site of impact for a few hours or even for a few days, after which many become symptom-free. However, up to one-half of all persons who injure their heads sufficiently to warrant hospitalisation develop chronic post-traumatic headaches. A small number of patients with headaches that persist after head injury have pain due to bleeding in the epidural, subdural or subarachnoid spaces, which is potentially lethal and needs urgent neurological attention. The headache of subdural haematoma begins at the time of trauma or the regaining of consciousness and persists, often for weeks or months, until the haematoma is removed. Blood in the subarachnoid space may induce headache, as may adhesions after head injury involving pain-sensitive structures in the arachnoid. However, most patients with post-traumatic headaches that persist or recur for long periods after head injury have no identifiable intracranial abnormalities to

explain their pain and some of these have a 'compensation neurosis' – a psychogenic type of pain.

Causalgia

Causalgia is a persistent burning pain, often in the mandible, that follows surgery or trauma. The cause is unclear and there is no good evidence that it is related to a peripheral nerve lesion or to psychogenic causes.

If a local anaesthetic injection relieves causalgia then cryoanalgesia may effect relief but neurosurgery may be required.

Frey syndrome

Frey syndrome (auriculotemporal syndrome, see Ch. 37) is a paroxysmal burning pain, usually in the temporal area or in front of the ear, associated with flushing and sweating on eating, which often follows parotid surgery and appears to be due to abnormal reinnervation.

Psychogenic causes of orofacial pain

The mouth and perioral soft tissues have among the richest sensory innervation in the body. Furthermore, a large part of the sensory homunculus on the cerebral cortex receives information from orofacial structures. Right from infancy, the mouth is concerned intimately with the psychological development of the individual, and disorders of structures such as the lips, teeth and oral mucosa can hold enormous emotional significance. It is hardly surprising, therefore, that there are a range of psychogenic types of orofacial pain.

In some studies, nearly 40% of the population have reported frequent headaches and orofacial pain. Four main groups of patients appear to suffer from psychogenic pain:

- normal individuals under extreme stress
- those with a personality trait such as hypochondriasis
- neurotic, often depressed persons
- rarely, psychotic patients.

Features common to most conditions with a psychogenic component, sometimes termed 'medically unexplained symptoms' (MUS), include:

- many are female
- constant chronic discomfort or pain
- pain often of a dull boring or burning type
- pain that is poorly localised (it may cross the midline to involve the other side or may move elsewhere)
- pain which rarely wakens the patient from sleep

- total lack of objective signs of organic disease
- all investigations are also negative
- there are often recent adverse 'life events' such as bereavement or family illness
- there are often multiple oral and/or other MUS, such as headaches, chronic back or neck pain, irritable bowel syndrome, insomnia, numbness or dysmenorrhoea
- cure is uncommon in most, yet few of those suffering seem to try or persist in using analgesics.

The reasons for MUS may include:

- possible links between neurohumoral mechanisms and altered CNS function
- the heightening of bodily sensations (lowered pain threshold) as a consequence of physiological processes such as autonomic arousal, muscle tension, hyperventilation, or inactivity
- misattribution of normal sensations to serious physical disorders.

Psychogenic (tension) headaches are common, especially in young adults. The headache, which is caused by anxiety or stress-induced muscle tension, affects the frontal, occipital and/or temporal muscles, and is felt as a constant ache or band-like pressure. The pain is often worse by the evening, but does not waken the patient. Reassurance may be effective, but the pain may be helped by massage, NSAIDs, or benzodiazepines, such as diazepam, as this is both anxiolytic and a mild muscle relaxant.

The most common types of orofacial pain with a strong psychogenic component are:

- atypical facial pain
- oral dysaesthesia (burning mouth syndrome)
- temporomandibular pain-dysfunction
- atypical odontalgia
- the syndrome of oral complaints.

Multiple pains and other complaints may occur simultaneously or sequentially and relief is rarely found (or admitted). Patients may bring diaries of their symptoms to emphasise their problem. Some have termed this the 'malady of small bits of paper' (*la maladie du petit papier*) and, though there is not always a psychogenic basis, such notes characterise patients with non-organic complaints. An anecdotal example is a 35-year-old woman who sequentially 'developed' right submandibular gland pain, right glossopharyngeal neuralgia (her words!), left glossopharyngeal neuralgia and left submandibular pain over a period of 15 years, during

which time she appeared not to develop signs of neurological disease or to deteriorate physically. On the other hand, written notes kept by the patient can be of considerable help to the clinician. Occasional patients quite deliberately induce painful oral lesions and some have Munchausen syndrome, where they behave in such a fashion as to appear to want operative intervention.

Referred causes of orofacial pain

Pain may occasionally be referred to the mouth, face or jaws from the following:

- Neck: cervical vertebral disease, especially cervical spondylosis, very occasionally causes pain referred to the face.
- Heart, in patients with angina: the latter pain usually affects the mandible, is initiated by exercise (especially in the cold) and abates quickly on rest.
- Lungs: orofacial pain emanating from lung cancer is a well-recognised entity and has been misdiagnosed as temporomandibular joint pain.
- Oesophagus: pain plus sialorrhoea may result from oesophageal lesions.
- Styloid process (stylalgia): Eagle syndrome, a rare disorder due to an elongated styloid process, may cause pain on chewing, swallowing or turning the head.
- Eyes: pain from the eyes can arise from disorders of refraction, retrobulbar neuritis (e.g. in multiple sclerosis), or glaucoma (raised intraocular pressure), and can radiate to the orbit or frontal region.
- Ears: middle-ear disease may cause headaches. Conversely, oral disease not infrequently causes pain referred to the ear, particularly from lesions of the posterior tongue. The classic picture is an elderly man with an undiagnosed tongue cancer who complains of earache.
- Pharynx: carcinoma of the pharynx may cause facial pain.

Diagnosis of orofacial pain

The cause of orofacial pain is established mainly from the history and examination findings but it is important to consider the usefulness of additional investigations, particularly imaging of the head and neck, using CT or MRI. It is important not to miss detecting organic disease and thus mislabelling the patient as having psychogenic pain (see Tables 9.2–9.4, Figs 9.2–9.4). Even patients with psychogenic disorders can suffer organic pain.

Table 9.3 Differential diagnosis of oral pain

Source of pain	Character	Exacerbating factors	Ability to locate signs	Associated with	Pain provoked by	Radiography
<i>Dental</i>						
Dental	Evoked, does not outlast	Hot/cold, sweet/sour	Poor	Caries, defective restorations, exposed dentine	Hot/cold, probing dentine	May show interproximal caries, defective restorations
Pulpal	Severe, intermittent, throbbing	Hot/cold, sometimes biting	Poor	Deep caries, extensive restoration	Hot/cold, probing, sometimes percussion	May show deep caries or deep restoration
<i>Periodontal</i>						
Periapical	For hours at same intensity; deep, boring	Biting	Good	Periapical swelling and redness, tooth mobility	Percussion, palpation of periapical area	Periapical views may show periapical changes
Lateral	For hours at same level, boring	Biting	Good	Periodontal, boring, deep pockets with pus exuding, tooth mobility	Percussion, palpation of periodontal area	Useful when x-rayed with probe inserted into pocket
Gingival	Pressing, annoying	Food impaction, toothbrushing	Good	Acute gingival inflammation	Touch, percussion	Not applicable
<i>Mucosal</i>						
Mucosal	Burning, sharp	Sour, sharp and hot food	Good	Erosive or ulcerative lesions, redness	Palpation	Not applicable

Table 9.4 Differentiation of important types of facial pain

	Idiopathic trigeminal neuralgia	Atypical facial pain	Migraine	Migrainous neuralgia
Age (years)	50	30–50	Any	30–50
Sex	F > M	F > M	F > M	M > F
Site	Unilateral, mandible or maxilla	± Bilateral, maxilla	Any, especially supraorbital	Retro-orbital
Associated features	–	± Depression	± Photophobia ± nausea ± vomiting	± Conjunctival injection ± lacrimation ± nasal congestion
Character	Lancinating	Dull	Throbbing	Boring
Duration	Brief (seconds)	Continual	Hours (usually daytime)	Few hours (usually night)
Precipitating factors	Trigger areas	None	± Foods	± Alcohol
Relieving factors	Carbamazepine	Antidepressants	Sumatriptan, clonidine; ergot derivatives	Oxygen, sumatriptan, clonidine, ergot derivatives, verapamil

Management of orofacial pain

Pain is the most important symptom suggestive of oral disease, but absence of pain does not exclude organic disease and presence of pain does not necessarily mean organic disease. There is also considerable individual variation in response to pain, and the threshold is lowered by tiredness, and psychogenic and other factors.

- Simple analgesics such as NSAIDs should be used initially, before embarking on more potent preparations. Chronic pain requires regular analgesia (not just as required). Details are given in Appendix 2.
- Antidepressants may help in pain of psychogenic origin.

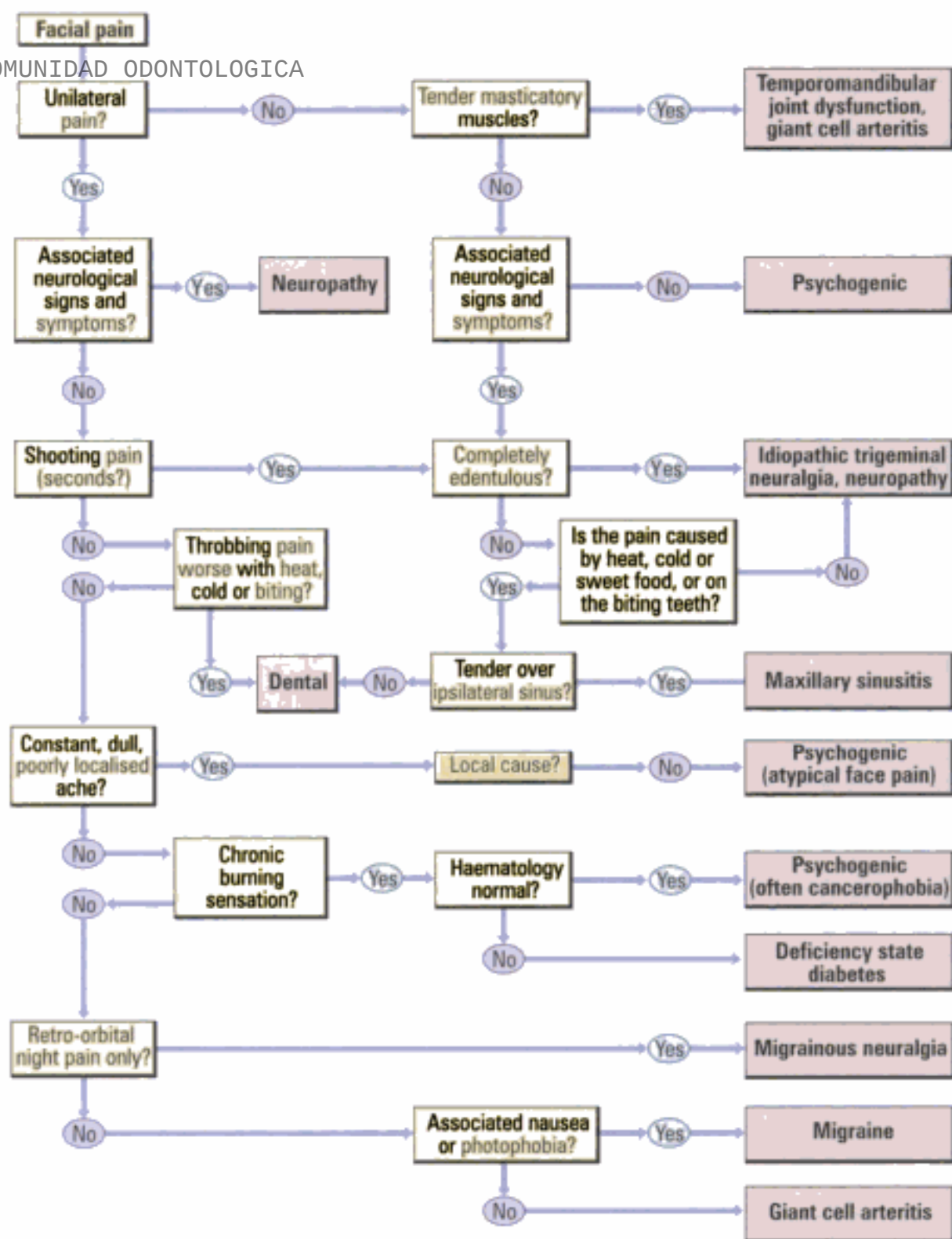


Figure 9.2 Algorithm for facial pain

- Anticonvulsants may help in neuropathic pain (neuralgias).
- Opioids may help in cancer pain.

It is important also:

- where possible, to identify and treat the cause of pain

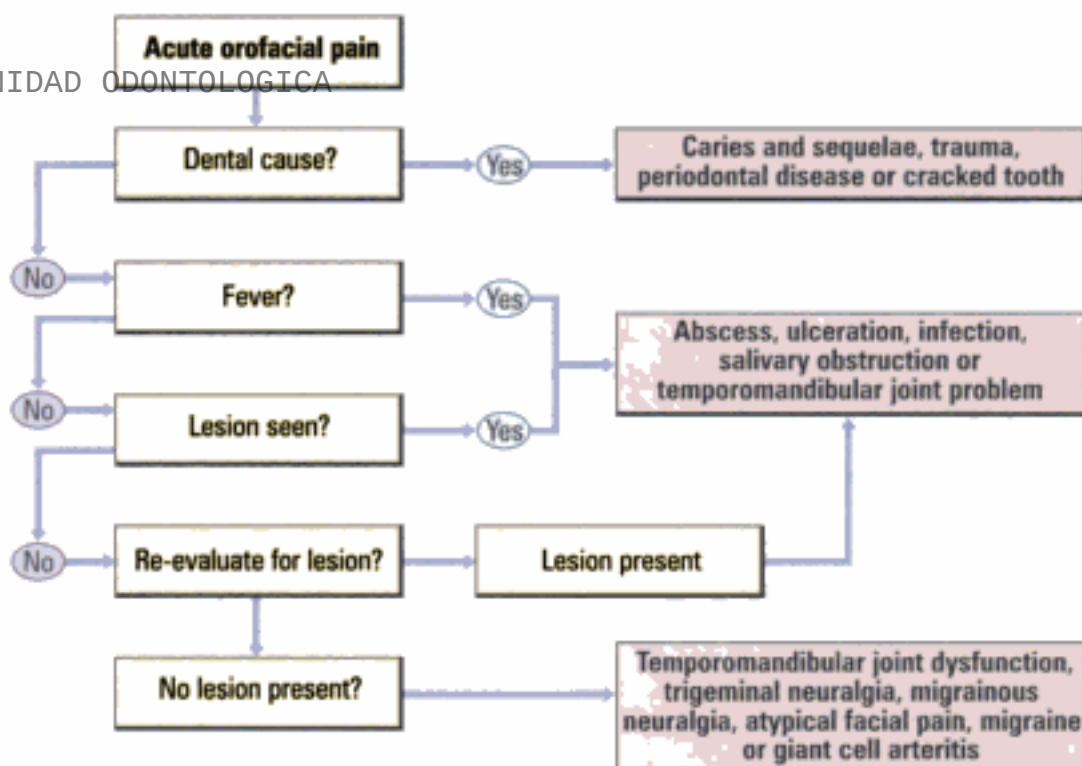


Figure 9.3 Algorithm for acute facial pain

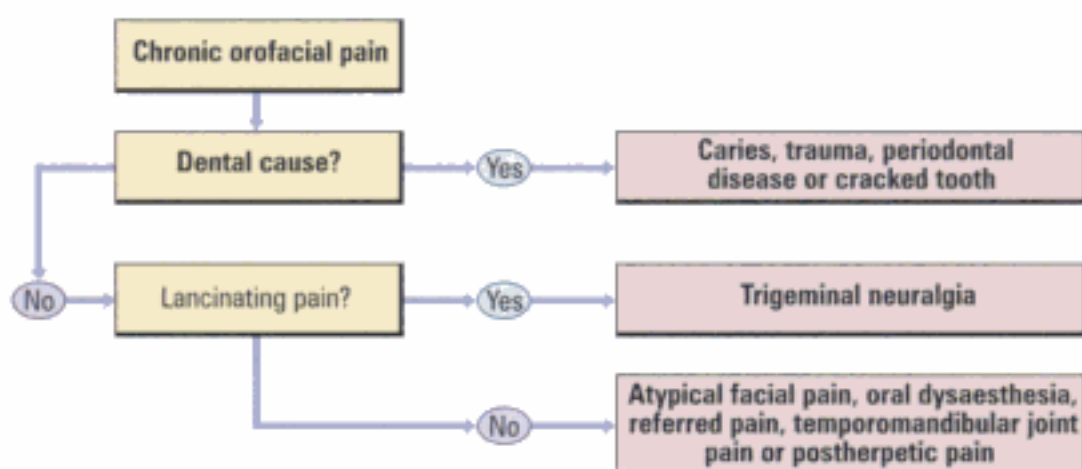


Figure 9.4 Algorithm for chronic facial pain

- equally it is useful to relieve factors which lower the pain threshold (fatigue, anxiety and depression)
- to avoid polypharmacy.

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10

PDFFREE COMUNIDAD ODONTOLOGICA

Red, White and Pigmented Lesions

KEY POINTS

Main causes of oral red lesions

- Inflammatory
- Reactive
- Erosive
- Atrophic
- Purpura
- Vascular
- Neoplasms

Main causes of white oral lesions

- Leukoedema
- Local causes
- Inherited (e.g. white sponge naevus)
- Leukoplakia
- Neoplasms
- Infections
- Mucocutaneous disease

Main causes of pigmented mucosal lesions

- Increased melanin:
 - racial
 - ephelis (freckle)
 - pigmentary incontinence
 - melanotic macules
 - naevus
 - malignant melanoma
 - Peutz-Jeghers syndrome
 - Addison's disease (and related disorders)
- Exogenous pigments:
 - amalgam or graphite tattoo
 - habits and drugs
 - heavy metals

Red lesions

Red oral lesions

These are commonplace and usually caused by inflammation in, for example, mucosal infections such as candidiasis (Fig. 10.1). However, they can also be sinister and signify severe dysplasia or malignant neoplasms. Red lesions can be:

- *Focal*: the lesion of most concern is erythroplasia, since it is usually dysplastic. Telangiectasia can also cause red lesions.
- *Multifocal*: these lesions are often caused by candidiasis.
- *Discoid*: these are prominent on the tongue in erythema migrans (geographic tongue).
- *Diffuse*: these lesions may be caused by mucositis, deficiency states and many infections, but candidiasis is the most common cause.
- *Linear*: these may be seen on the tongue in deficiency states.

Causes of red oral lesions

Mucosal inflammation

Most red lesions are inflammatory. The most common are (Table 10.1):

- **Viral stomatitis**: erythema is seen with most oral viral infections (e.g. herpes simplex stomatitis).
- **Candidiasis**:
 - denture-related stomatitis is a form of mild chronic atrophic candidiasis consisting of inflammation of the mucosa beneath a denture (usually a complete upper denture), such that the hard palate is red (Fig. 10.1)
 - acute oral candidiasis may complicate corticosteroid or antibiotic



Figure 10.1 Denture-related stomatitis; red lesions are usually inflammatory in origin, but related erythroplasia must be excluded, since it is potentially malignant

Table 10.1 More comprehensive table of causes of red lesions**Localised**

- Inflammatory
- Candidiasis
- Other mycoses
- Reiter's disease
- Graft-versus-host disease
- Drugs
- Epithelioid angiomatosis
- Reactive lesions:
 - pyogenic granulomas
 - peripheral giant cell granulomas
- Atrophic
- Geographic tongue
- Lichen planus
- Lupus erythematosus
- Erythroplasia
- Burns
- Avitaminosis B₁₂
- Purpura

Localised – Contd

- Vascular
- Telangiectases (hereditary haemorrhagic telangiectasia or scleroderma)
- Angiokeratomas (Fabry's disease)
- Angiomas
- Neoplasms
- Giant cell tumour
- Squamous carcinoma
- Kaposi sarcoma
- Wegener's granulomatosis

Generalised

- Candidiasis
- Avitaminosis B complex (rarely)
- Irradiation or chemotherapy-induced mucositis
- Polycythaemia

therapy, particularly with long-term, broad-spectrum antimicrobials, and causes widespread erythema and soreness of the oral mucosa, sometimes with thrush

median rhomboid glossitis is usually detected by the patient or dentist as a persistent red, rhomboidal depapillated area in the midline of the dorsum of the tongue.

- Deep mycoses, which are rare in the developed world, except in HIV disease and other immunocompromised persons:
 - histoplasmosis
 - cryptococcus
 - blastomycosis
 - paracoccidioidomycosis.
- Radiation mucositis is common after irradiation of tumours of the head and neck, if the radiation field involves the oral mucosa. Arising within 3 weeks of the irradiation, there is generalised erythema, and sometimes ulceration.
- Immunological reactions such as plasma cell gingivostomatitis, granulomatous disorders (sarcoidosis, Crohn's disease, orofacial granulomatosis), amyloidosis and graft-versus-host disease.

Reactive lesions

These are caused by pyogenic granulomas and peripheral giant cell granulomas.

Erosions

These are caused by burns and vesiculobullous disorders such as lichen planus, erythema multiforme and pemphigus.

Atrophy

These are caused by:

- erythroplasia – one of the more important causes of a localised red lesion, since it is often dysplastic
- erythema migrans – manifests with irregular depapillated red areas, which change in size and shape, usually in the dorsum of the tongue
- lichen planus – may present with atrophic red areas in some forms
- desquamative gingivitis (see Ch. 37) – is a frequent cause of red gingivae, almost invariably caused by lichen planus or pemphigoid
- iron or vitamin deficiency states – may cause glossitis or other red lesions.

Purpura

Bleeding into the skin and mucosa is usually caused by (Table 10.2):

- Trauma: occasional small traumatic petechiae at the occlusal line are seen in otherwise healthy patients.
- Suction (e.g. fellatio may produce bruising in the soft palate).
- A blood platelet disorder: red or brown pinpoint lesions (petechiae) or diffuse bruising (ecchymoses) are seen, mainly at sites of trauma, such as at the junction of the hard and soft palate (and often extra-orally).
- Localised oral purpura or angina bullosa haemorrhagica: an idiopathic, fairly common, cause of purpura or blood blisters, seen only in the mouth, pharynx or oesophagus, mainly in the soft palate, in older persons.

Vascular anomalies (angiomas and telangiectasia)

These can be caused by:

- Dilated lingual veins (varices): these may be conspicuous in the elderly in the ventrum of the tongue and may cause unnecessary alarm. Similar lesions may be seen in the lip.
- Haemangiomas: these are usually small isolated developmental anomalies, or hamartomas. Rarely, orofacial angiomas may be part of the

Table 10.2 Causes of oral purpura

- Trauma
- Suction or trauma from:
 - appliances
 - habits
 - fellatio
 - cunnilingus
 - vomiting
- Platelet disorders
 - autoimmune thrombocytopenia (ITP; idiopathic thrombocytopenic purpura)
 - bone marrow disorders
 - aplastic anaemia
 - leukaemia
 - infections:
 - infectious mononucleosis
 - rubella
 - HIV infection
- Gammopathies
- Rare disorders
- Localised oral purpura (angina bullosa haemorrhagica)
- Vascular disorders
- Scurvy
- Ehlers–Danlos syndrome
- Amyloidosis

Sturge–Weber syndrome (haemangioma with epilepsy and hemiplegia; see Ch.25).

- Telangiectasias (dilated capillaries): these may be seen after irradiation of the mouth and in various systemic disorders such as hereditary haemorrhagic telangiectasia and systemic sclerosis.

Neoplasms

Red neoplasms include:

- peripheral giant cell tumours
- angiosarcomas such as Kaposi sarcoma – a common neoplasm in HIV/AIDS, appears in the mouth as red or purplish areas or nodules, especially seen on the palate
- squamous cell carcinomas
- Wegener's granulomatosis
- midline granulomas.

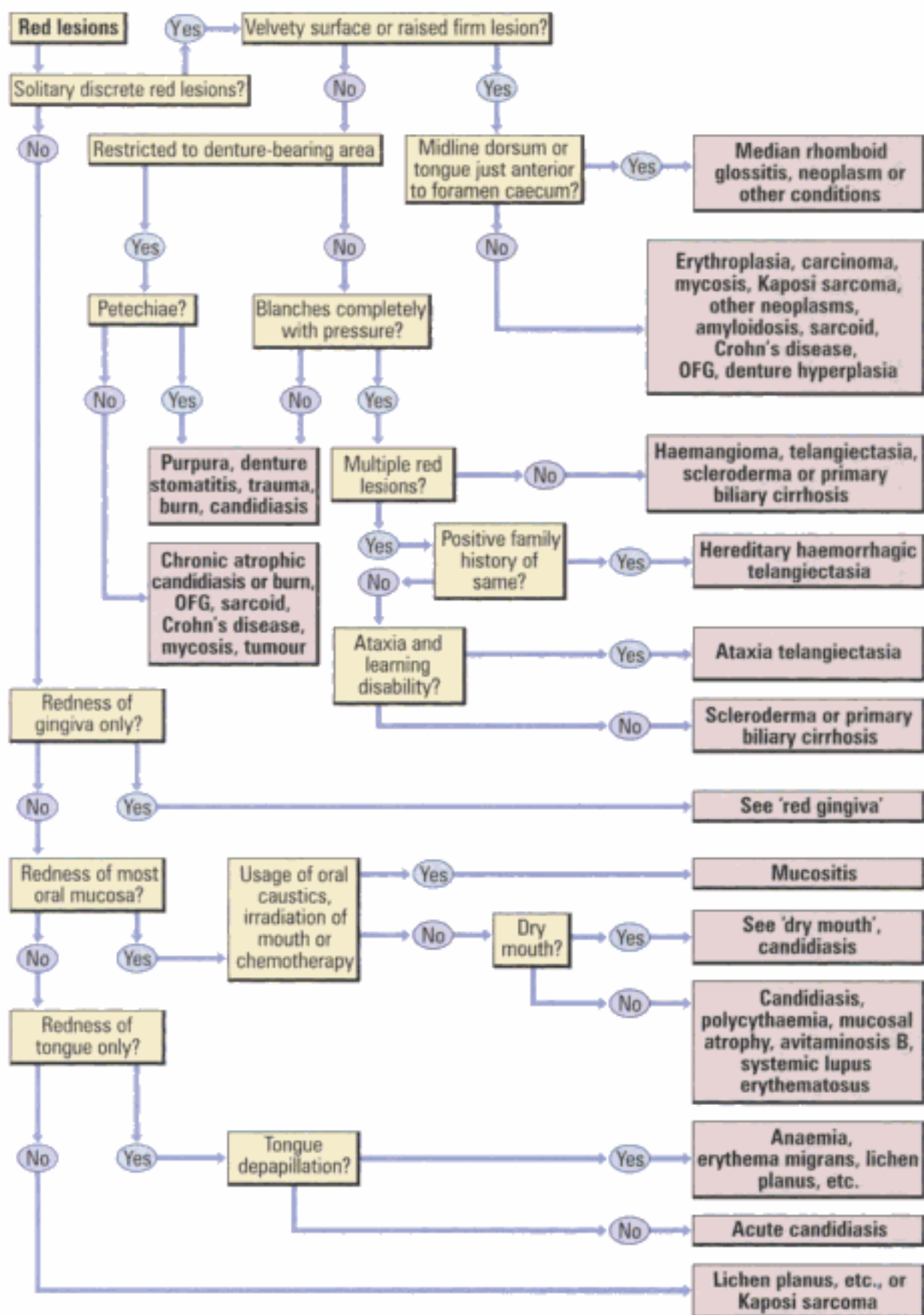


Figure 10.2 Algorithm for red lesions. (OFG, orofacial granulomatosis)

Diagnosis

Diagnosis of red lesions is mainly clinical; lesions should also be sought on the skin or other mucosae. Haematological tests and/or biopsy or imaging may be indicated. It may be necessary to take a blood picture (including blood and platelet count) and assess haemostatic function or exclude vitamin deficiencies (Fig. 10.2).

Management

Treatment is of the underlying cause or by excision or laser.

White lesions

Some common conditions, notably Fordyce granules (see Ch. 25) are yellowish rather than white in colour, but may cause diagnostic confusion. Collections of debris (materia alba) or fungi (candidiasis) may also look white, but these can usually easily be wiped off with a gauze. Other lesions appear white usually because they are composed of thickened keratin, which looks white when wet. These lesions, being inherent in the mucosa, will not easily wipe away with a gauze swab (Fig. 10.3).

White lesions are usually painless, but can be focal, multifocal, striated or diffuse, and these features may give a guide to the diagnosis. For example:

- focal lesions are often caused by keratoses
- multifocal lesions are common in thrush (pseudomembraneous candidiasis) and lichen planus
- striated lesions are typical of lichen planus
- diffuse white areas are seen in the buccal mucosa in leukoedema, and in the palate in stomatitis nicotinia.



Figure 10.3 Leukoplakia on the gingiva; white lesions are usually benign, but dysplasia must be excluded since this suggests a lesion is potentially malignant

Main causes of white oral lesions (Table 10.3)

- Leukoedema.
- Local causes:
 - materia alba (debris from poor oral hygiene)
 - keratoses (e.g. frictional keratosis (and cheek/lip biting), smoker's keratosis and snuff-dipper's keratosis)
 - burns
 - grafts
 - scars
 - furred or hairy tongue.
- Inherited (e.g. white sponge naevus).
- Leukoplakia:
 - homogeneous
 - non-homogeneous, either nodular (verrucous) or speckled (erythroleukoplakia).
- Neoplasms:
 - carcinoma
 - verruciform xanthoma.
- Infections:
 - candidiasis (thrush: candidal leukoplakia)

Table 10.3 More comprehensive table of causes of oral white lesions

Neoplastic and possibly pre-neoplastic

- Leukoplakia
- Keratoses
- Carcinoma

Inflammatory

- Infective:
 - candidiasis
 - hairy leukoplakia
 - syphilitic mucous patches and keratosis
 - Koplik's spots (measles)
 - some papillomas
 - Reiter's disease
 - koilocytic dysplasia (papilloma virus)
- Non-infective:
 - lichen planus
 - lupus erythematosus

Others

- Cheek-biting
- Materia alba (debris)
- Burns
- Grafts
- Scars
- Verruciform xanthoma

Congenital

- Leukoedema
- Fordyce spots
- White sponge naevus
- Focal palmoplantar and oral mucosa hyperkeratosis syndrome
- Darier's disease
- Pachyonychia congenita
- Dyskeratosis congenita

Epstein-Barr virus (hairy leukoplakia)

human papilloma virus (koilocytic dysplasia, warts, papillomas)

syphilis (syphilitic mucous patches and keratosis)

measles (Koplik's spots).

● Mucocutaneous disease:

lichen planus

lupus erythematosus.

Diagnosis

Diagnosis of white lesions is mainly clinical; lesions should also be sought on the skin or other mucosae. Haematological tests and/or biopsy or imaging may be indicated (Fig. 10.4).

Management

Treatment is of the underlying cause, or excision.

Hyperpigmentation

Oral mucosal discoloration which ranges from brown to black may be due to superficial (extrinsic) or deep (intrinsic in or beneath mucosa) causes.

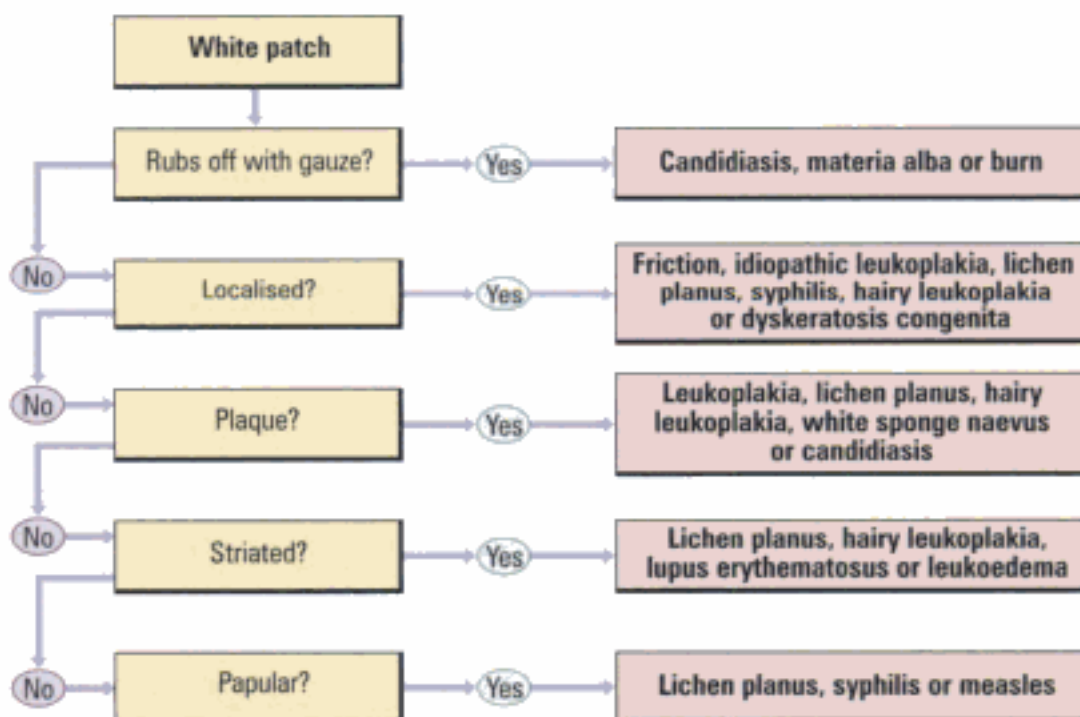


Figure 10.4 Algorithm for white lesions

Causes

Extrinsic discoloration

Extrinsic discoloration is rarely of consequence and is usually caused by coloured foods, drinks or drugs. Frequently, both mucosae and teeth are discolored.

- Foods and beverages, such as beetroot, red wine, coffee and tea.
- Confectionery, such as liquorice.
- Drugs, such as chlorhexidine, iron salts, griseofulvin, crack cocaine, minocycline, bismuth subsalicylate, lansoprazole and HRT.
- Tobacco: this may cause extrinsic discoloration, but can also cause intrinsic pigmentary incontinence, with pigment cells increasing and appearing in the lamina propria. This is especially likely in persons who smoke with the lighted end of the cigarette within the mouth (reverse smoking), as practised mainly in some Asian communities.
- Betel: this may cause a brownish-red discoloration, mainly on the teeth and in the buccal mucosa, with an irregular epithelial surface that has a tendency to desquamate. It is seen mainly in women from South and Southeast Asia. Betel chewer's mucosa epithelium is often hyperplastic, and brownish amorphous material from the betel quid may be seen on the epithelial surface and intra- and intercellularly, with ballooning of epithelial cells. Betel chewer's mucosa is not known to be precancerous, but betel use predisposes to submucous fibrosis and to cancer.

Black hairy tongue

This is discussed in Chapter 37.

Intrinsic staining

Increased melanin or number of melanocytes, or other materials can cause intrinsic (endogenous) hyperpigmentation. Intrinsic discoloration may have more significance than the extrinsic type. Normal intrinsic pigmentation is due to melanin, produced by melanocytes – dendritic cells prominent in the basal epithelium. This originates from the amino acid tyrosine, which is converted to dihydroxyphenylalanine (DOPA) and thence to melanin. The colour can vary from brown to blue or black, depending on the amount and location of the melanin. Generalised pigmentation, often affecting the gingivae mainly, is common in persons of colour, and is racial.

Localised areas of pigmentation are usually caused by benign conditions:

- embedded amalgam (amalgam tattoo) (Fig. 10.5)
- embedded graphite (graphite tattoo)
- other foreign bodies
- local irritation/inflammation



Figure 10.5 Amalgam tattoo; by far the most common cause of an isolated hyperpigmented lesion

- melanotic macule
- naevi
- melanoacanthoma.

However, neoplasms such as Kaposi sarcoma or malignant melanoma are occasionally responsible.

The anterior pituitary gland releases melanocyte stimulating hormone (MSH), which increases melanin production. Melanin pigmentation thus increases under hormonal stimulation, either by MSH, or in pregnancy, or rarely due to the action of adrenocorticotrophic hormone (ACTH) which molecule is similar to MSH, or under the influence of other factors (e.g. smoking). Thus in all patients systemic causes should be excluded, such as:

- drugs; including smoking and the contraceptive pill
- hypoadrenalism; there is increased ACTH production
- Peutz-Jeghers syndrome
- HIV infection
- Von Recklinghausen's disease
- Albright syndrome
- rarely, palatal pigmentation from bronchogenic carcinoma.

Causes

Causes of oral pigmentation include (see Table 2.4):

- **Racial pigmentation:** this is the most usual cause of patchy or generalised brown oral mucosal pigmentation, caused by melanin. Seen mainly in blacks and Asians it can also be noted in patients of Mediterranean descent, sometimes even in some fairly light-skinned people. It is most obvious in the anterior labial gingivae and palatal mucosa, and the pigmentation is usually symmetrically distributed.

Patches may be seen elsewhere. Pigmentation may be first noted by the patient in adult life and then incorrectly assumed to be acquired rather than congenital in origin.

- Chronic inflammation, such as in lichen planus, can result in melanin drop-out, especially in persons with pigmented skin. The oral pigmentation (pigmentary incontinence) is often gingival or buccal.
- Amalgam tattoo: this is the most common cause of a single patch of macular blue-black pigmentation, does not change significantly in size or colour, is painless and is usually seen in the mandibular gingiva or at least close to the teeth scar of an apicectomy where there has been a retrograde root-filling. Amalgam tattoo is best excised to exclude naevi or melanoma.
- Graphite tattoo: this may be seen, for example, where a pencil lead has been broken off in the mucosa.
- Melanotic macules: these are usually single, brown, collections of melanin-containing cells. Melanotic macules are flat and mostly smaller than 1 cm and contain increased melanin, do not change rapidly in size or colour, are painless and are seen particularly on the vermilion border of the lip and on the palate. They are seen mainly in white people and are innocuous. Most arise slowly, but occasionally they rapidly appear. They are best removed to exclude melanoma.
- Naevi: these are blue-black often papular lesions formed from increased melanin-containing cells (naevus cells) and are usually smaller than 1 cm. Some 60% are raised, they do not change rapidly in size or colour, are painless and are seen particularly on the palate. Approximately half of naevi are histologically of the intradermal (intra-mucosal) type when the melanin is in the lamina propria, one-third are blue naevi, others are compound naevi, and some are junctional. There is no evidence that most naevi, except rare junctional naevi, progress to melanoma. However, they may resemble melanomas and are best removed to exclude melanoma.
- Melanoacanthoma: in some adults of African descent, larger lesions, from 5 mm to 2 cm in diameter, termed 'melanoacanthomas' may be seen. These are seen mainly in the buccal mucosa or palate in females, may appear rapidly, and are probably reactive lesions. They are best removed.
- Malignant melanoma: this is rare but may arise in apparently normal mucosa or in a pre-existent pigmented naevus, usually in the palate or maxillary gingivae. About one-third of melanomas arise in areas of hyperpigmentation. Features suggestive of malignancy include a rapid increase in size, change in colour, ulceration, pain, the occurrence of satellite pigmented spots or regional lymph node enlargement. However, up to 15% of melanomas are amelanotic. Superficial melanomas have a

better prognosis than nodular ones. Radical excision is indicated for treatment of melanomas.

- Kaposi sarcoma (see Chs 37 and 38).

- Drugs: generalised hyperpigmentation or pigmentation may be induced sometimes with pigmentation of skin or other areas.

Smoking tobacco is now a fairly common cause (smoker's melanosis).

Antimalarials produce a variety of colours in the mucosa, ranging from yellow with mepacrine to blue-black with amodiaquine.

ACTH therapy may produce brown pigmentation.

Busulphan, some other cytotoxic drugs, oral contraceptives, phenothiazines and anticonvulsants may also occasionally produce, or increase, brown pigmentation.

Minocycline may cause blackish discoloration of the teeth, gingivae and bone, skin, sclera and even breast milk.

Gold may produce purplish gingival discoloration.

Many of the other heavy metals formerly implicated in producing oral pigmentation (such as mercury, lead and bismuth) are not used therapeutically now, although industrial exposure still occurs rarely.

Metallic sulphides deposited in the tissues were seen especially where oral hygiene was poor, and bacteria produced sulphides, resulting in pigmentation at the gingival margin (e.g. lead line).

- Addison's disease (hypoadrenalism): this is uncommon, but may cause generalised or patchy hyperpigmentation due to excessive production of ACTH which has activities similar to MSH. Addison's disease (adrenocortical hypofunction) is usually autoimmune (idiopathic).

Hyperpigmentation is generalised, but is most obvious in areas normally pigmented (e.g. the areolae of nipples, genitalia), skin flexures and sites of trauma. The oral mucosa may show patchy hyperpigmentation. Patients with Addison's disease also typically have weakness and weight loss, and hypotension.

- Nelson syndrome: this is a rare condition caused by ACTH overproduction in response to adrenalectomy, usually for breast cancer.
- ACTH-producing tumours: brown pigmentation, particularly of the soft palate, and may be an oral manifestation of a rare ACTH-producing neoplasm such as a bronchogenic carcinoma.
- Peutz-Jeghers syndrome: in this rare autosomal-dominant condition, oral and circumoral patchy brown pigmentation is seen with small-intestinal polyps.

Diagnosis

The nature of hyperpigmentation can sometimes only be established after further investigation (Fig. 10.6).

Patients with generalised or multiple hyperpigmentation

- Blood pressure should be taken to exclude Addison's disease (hypotension is characteristic).
- Plasma cortisol levels may be indicated to exclude Addison's disease (low levels found).
- A Synacthen test may be indicated to exclude Addison's disease (impaired response to adrenocorticotrophic hormone found).

Patients with localised hyperpigmentation

- Radiographs may be helpful, as they can sometimes show amalgam, graphite or a foreign body, or bone rarefaction in pigmented neuroectodermal tumour of infancy.
- Photographs may be useful for future comparison of size and colour.
- Urinary catecholamines: if a pigmented neuroectodermal tumour is suspected the catecholamines are raised.
- Biopsy may be indicated. If early detection of oral melanomas is to be achieved, all pigmented oral cavity lesions should be viewed with suspicion. The consensus of opinion is that a lesion with the following clinical features is *seriously* suggestive of being a malignant melanoma and is best biopsied at the time of definitive operation:
 - a solitary raised lesion
 - a rapid increase in size
 - change in colour
 - ulceration
 - pain
 - evidence of satellite pigmented spots
 - regional lymph node enlargement.

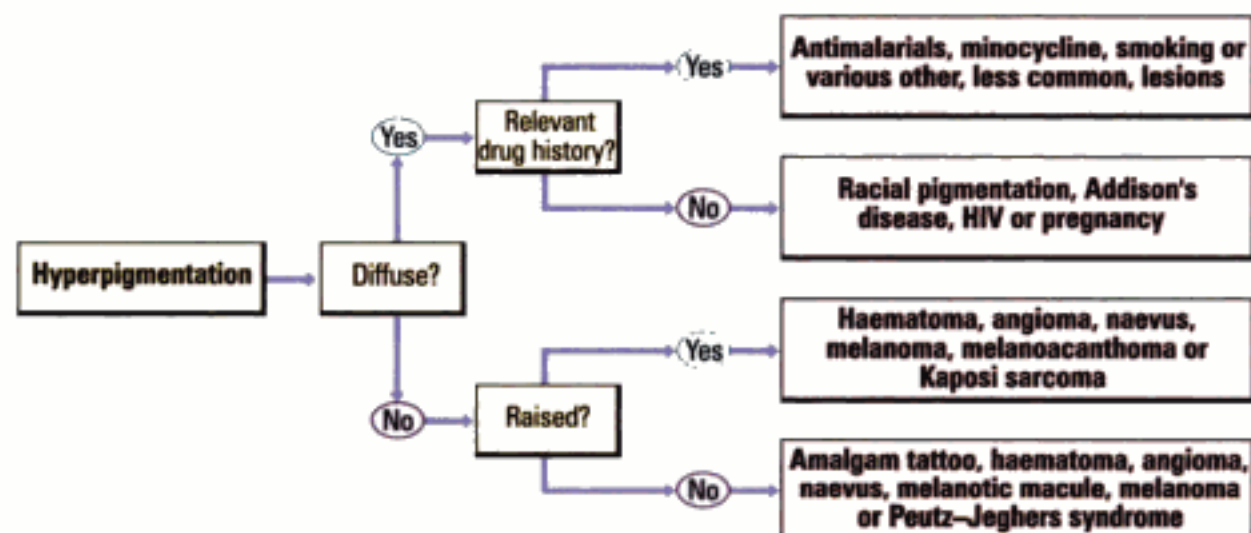


Figure 10.6 Algorithm for hyperpigmented lesions

Management

Management is of the underlying condition. Excision biopsy of isolated hyperpigmented lesions is often recommended to exclude malignancy, because of the malignant potential of some (particularly the junctional naevus) and for cosmetic reasons. This is particularly important if the lesions are raised or nodular or have clinical features as above seriously suggestive of being malignant melanoma.

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Sensory and Motor Changes

Main causes of orofacial sensory or motor changes

Sensory changes

- **Extracranial:**
 - trauma (e.g. surgical, fractures)
 - bone disease
 - drugs
 - diabetes
 - neoplastic
- **Intracranial:**
 - trauma (e.g. surgical, fractures)
 - inflammatory
 - neoplastic
 - cerebrovascular disease
 - diabetes
 - bone disease
 - psychogenic
 - drugs
 - multiple sclerosis

Motor changes (paralysis)

- **Upper motor neurone lesion:**
 - cerebrovascular accident
 - others
- **Lower motor neurone lesion:**
 - systemic infection
 - Bell's palsy (herpes simplex virus usually)
 - middle ear disease
 - parotid lesion
 - trauma to branch of facial nerve
 - others

Sensory changes

Normal facial sensation, mediated by the trigeminal nerve, is important to protect the skin, mucosae and especially the cornea from damage. Facial sensory changes, which can be caused by lesions of a sensory branch of

the trigeminal nerve or the central connections (Fig. 11.1), may include sensory awareness that is:

- completely lost (anaesthesia)
- partially lost (hypoaesthesia)
- altered (paraesthesia) – often ‘pins and needles’ or similar discomfort – it may arise during recovery of nerve damage.

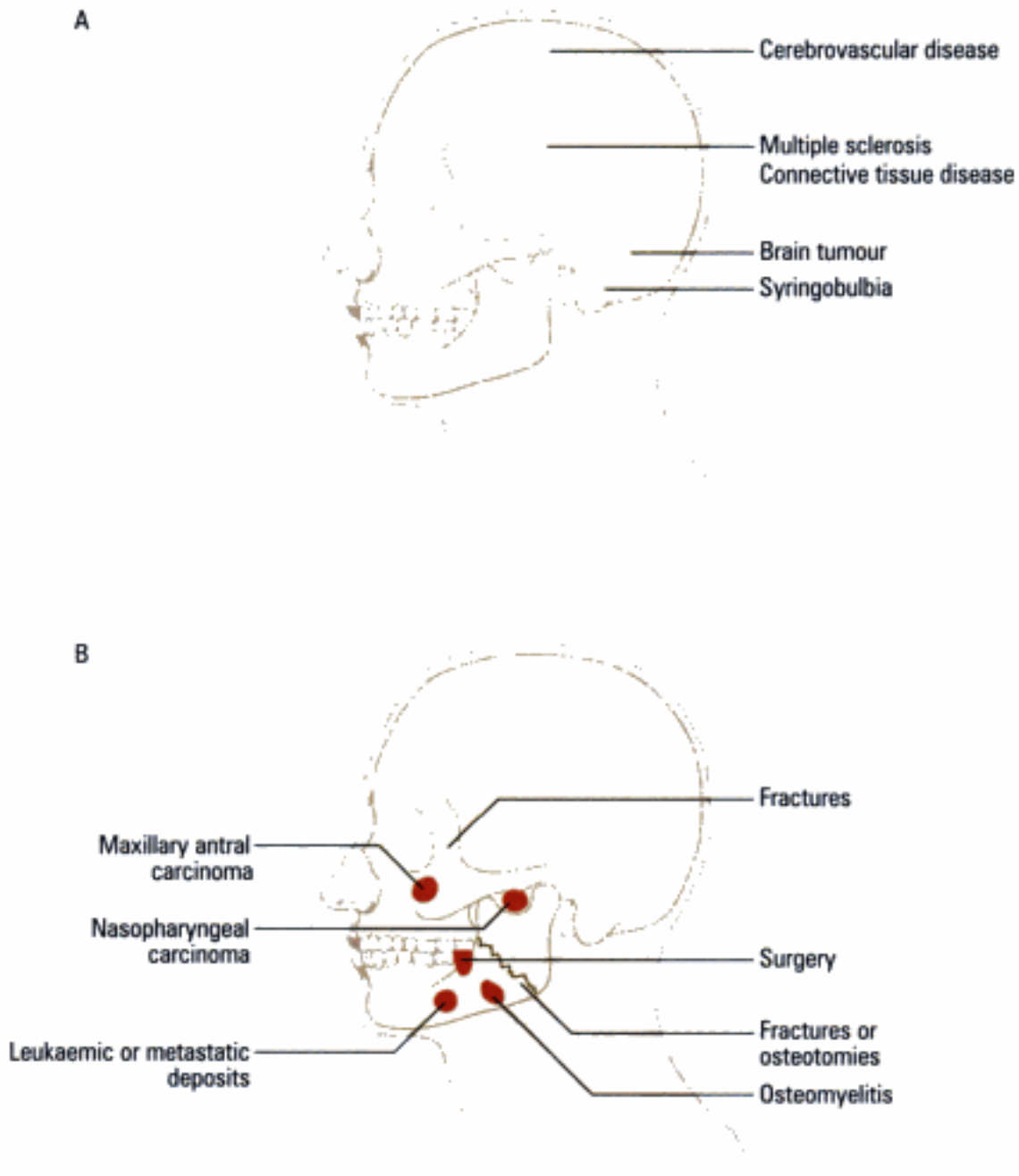


Figure 11.1 Causes of sensory loss: A, intracranial; B, extracranial

Testing trigeminal function

PDFFREE.COM Trigeminal functions that should be tested include:

- Corneal reflex (this tests fifth and seventh cranial nerves); touching the cornea gently with sterile cotton wool should produce a blink.
- Skin sensation, by using:
 - light touch (cotton wool)
 - pin point (sterile needle)
 - temperature
 - vibration
 - two-point discrimination.
- Motor function by palpating:
 - muscles of mastication during function
 - masseters during clenching
 - temporalis during clenching
 - pterygoids during jaw protrusion
 - jaw jerk.

Causes of lesions of a sensory branch of the trigeminal nerve (Table 11.1)

Extracranial causes

Extracranial causes of facial sensory loss are most common and include damage to the trigeminal nerve from the following causes.

Trauma

This is the usual cause – especially after orthognathic or cancer surgery. If the nerves are stretched or compressed (neuropraxia), there is often only hypoaesthesia, and recovery of sensation is speedy, typically within days. However, if the nerves are severed (neurotmesis), anaesthesia is profound and recovery is delayed for months and accompanied by paraesthesia or hyperaesthesia. Recovery is sometimes not complete.

- Trauma to the mandibular division can have a variety of causes:
 - inferior alveolar local analgesic injections
 - fractures of the mandibular body or angle
 - surgery (particularly surgical extraction of lower third molars, osteotomies or jaw resections) or even endodontics.
- Damage to the mental nerve can have a variety of causes:
 - operations in the region
 - pressure from a denture – the mental foramen is close beneath a lower denture and there is anaesthesia of the lower lip on the affected side.
- The lingual nerve may be damaged, especially during removal of lower third molars, particularly when the lingual split technique is used. Ipsilateral lingual hypoaesthesia or anaesthesia usually result.

Table 11.1 More comprehensive table of causes of facial sensory loss**Intracranial**

- Trauma (e.g. surgical treatment of trigeminal neuralgia)
- Inflammatory:
 - multiple sclerosis
 - sarcoidosis
 - connective tissue disorders
 - infections – neurosyphilis, HIV infection, herpesviruses, tuberculosis, leprosy
- Neoplastic – cerebral tumours
- Syringobulbia
- Vascular:
 - cerebrovascular disease
 - aneurysms
- Drugs:
 - labetalol
 - ritonavir
 - stilbamidine
 - mefloquine
 - others
- Bone disease:
 - Paget's disease
 - osteopetrosis

Extracranial

- Trauma (e.g. surgical, fractures) to inferior dental, lingual, mental or infraorbital nerves
- Inflammatory:
 - osteomyelitis
- Neoplastic:
 - carcinoma of antrum or nasopharynx
 - metastatic tumours
 - leukaemic deposits

Benign trigeminal neuropathy

- Idiopathic

Psychogenic

- Hysteria
- Hyperventilation syndrome

Endocrine disease

- Diabetes

- Damage to branches of the maxillary division of the trigeminal nerve may be caused by trauma (usually Le Fort II or III middle-third facial fractures).

Bone disease

- Osteomyelitis in the mandible may affect the inferior alveolar nerve to cause labial anaesthesia.
- Paget's disease.
- Malignant disease may be the cause. Such as:
 - Oral carcinomas that may invade the jaws to cause anaesthesia. Central malignancies such as osteosarcoma may produce a similar pattern.
 - Nasopharyngeal carcinomas that may: invade the pharyngeal wall to infiltrate the mandibular division of the trigeminal nerve, causing pain and sensory loss in the region of the inferior alveolar, lingual and auriculotemporal nerve distributions; invade the levator palati to

cause soft palate immobility; and, by occluding the Eustachian tube, cause deafness (Trotter syndrome).

Leukaemia, myeloma or metastases (usually from breast, lung, stomach or colon cancer) that may cause deposits in the mandible and labial hypoaesthesia.

Carcinoma of the maxillary antrum that may produce ipsilateral upper labial hypoaesthesia or anaesthesia.

Neuropathies

- Disseminated (multiple) sclerosis.
- Diabetes.
- Drug induced.

Intracranial lesions

Intracranial lesions affecting the trigeminal nerve or connections are uncommon but serious. They include:

- Inflammatory disorders:
 - disseminated sclerosis
 - sarcoidosis
 - infections (e.g. HIV, syphilis)
 - connective tissue disorders.
- Cerebrovascular disease:
 - since other cranial nerves are anatomically close, there may be associated neurological deficits in intracranial causes of facial sensory loss
 - in posterior cranial fossa lesions, for example, there may be cerebellar features such as ataxia
 - in middle cranial fossa lesions there may be associated neurological deficits affecting cranial nerve VI and thus mediolateral eye movements.
- Neoplasms, such as brain tumours (often metastases).
- Syringobulbia: this leads to sensory loss spreading from the periphery of the face inwards towards the nose, plus a lower motor nerve lesion of the vagus, hypoglossal and accessory nerves, leading to disturbances of speech and swallowing, and bilateral upper motor neurone lesions affecting all limbs.
- Drugs.
- Hysteria.

Benign trigeminal neuropathy

This is a transient sensory loss in one or more divisions of the trigeminal nerve. It seldom occurs until the second decade or affects the corneal

reflex. The aetiology is unknown, though some patients prove to have connective tissue disorder.

Psychogenic causes of facial sensory loss

Hysteria, and particularly hyperventilation syndrome, may underlie some causes of facial anaesthesia/hypoaesthesia. Typically the 'anaesthesia' is bilateral and associated with bizarre neurological complaints.

Diagnosis

In view of the potential seriousness of facial sensory loss, a full neurological assessment must be undertaken, unless the loss is unequivocally related to local trauma (Fig. 11.2). Possible investigations include:

- imaging (panoral, occipitomeatal, lateral and postero-anterior skull, and MRI/CT)
- a full blood count, erythrocyte sedimentation rate, random sugar, and syphilis serology.

Management

If there has been neurotmesis, surgical correction can achieve good results. In benign, reversible causes, the underlying cause should be corrected, and the patient reassured that there should be some if not full return of sensation over the subsequent 18 months. If the cornea is anaesthetic or

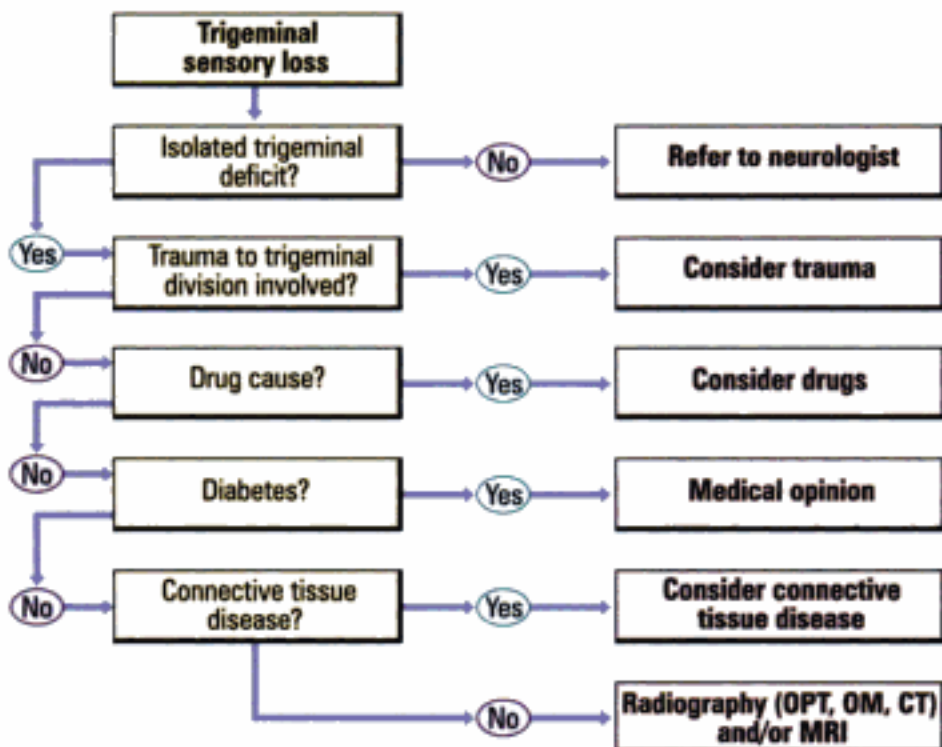


Figure 11.2 Algorithm for sensory loss

hypoaesthetic, an eye pad should be worn over the closed eyelids, since the protective corneal reflex is lost and the cornea may be damaged.

Motor changes

Facial paralysis

Facial movements may be impaired (palsy), increased or abnormal. In any event, this causes a major cosmetic problem and is very distressing for the patient.

- The facial nerve (seventh cranial) is the motor nerve to the stylohyoid and stapedius muscles and muscles of facial expression, including the:
 - orbicularis oculi
 - orbicularis oris
 - buccinator
 - platysma
 - scalp and auricle muscles.
- The facial nerve has, besides these motor components:
 - secretomotor fibres
 - nervus intermedius, associated with taste perception
 - sensory component.
- Facial paralysis (palsy) can be very disfiguring, since the ability to smile is impaired.
- Lesions of the facial nerve central connections (supranuclear or upper motor neurone lesions) or the facial nerve itself (nuclear and infranuclear or lower motor neurone lesions), or muscle disease, can lead to facial weakness.

Causes

Upper motor neurone (UMN) lesions give a palsy which affects mainly the lower parts of the face, since there is bilateral innervation of the upper third of the face. UMN lesions may be due to (Table 11.2 and Fig. 11.3):

- stroke, commonly due to haemorrhage or thrombosis in or around the internal capsule
- a focal lesion which may be moderately selective or cause a cerebral palsy
- a cortical lesion of the cerebral hemispheres, but only rarely.

Lower motor neurone (LMN) lesions give a palsy which affects both the upper and lower parts of the face. Although there is bilateral innervation of the upper third of the face, there is only one common path in the LMN. LMN lesions may be due to:

- **Facial nucleus lesions;** such as poliomyelitis, but only rarely.
- **Pontine or posterior cranial fossa lesions.** As there are a large number of tracts in close approximation in the pons, the features may be diffuse with frequent bilateral or contralateral involvement. The sixth and eighth cranial nerves are often involved along with the seventh nerve and serve as a good localising feature in facial palsy. The causes could be:
 - disseminated sclerosis
 - pseudobulbar palsy
 - neoplasm (acoustic neuroma, or even more rarely a meningioma)
 - vascular lesion (basilar artery aneurysm)

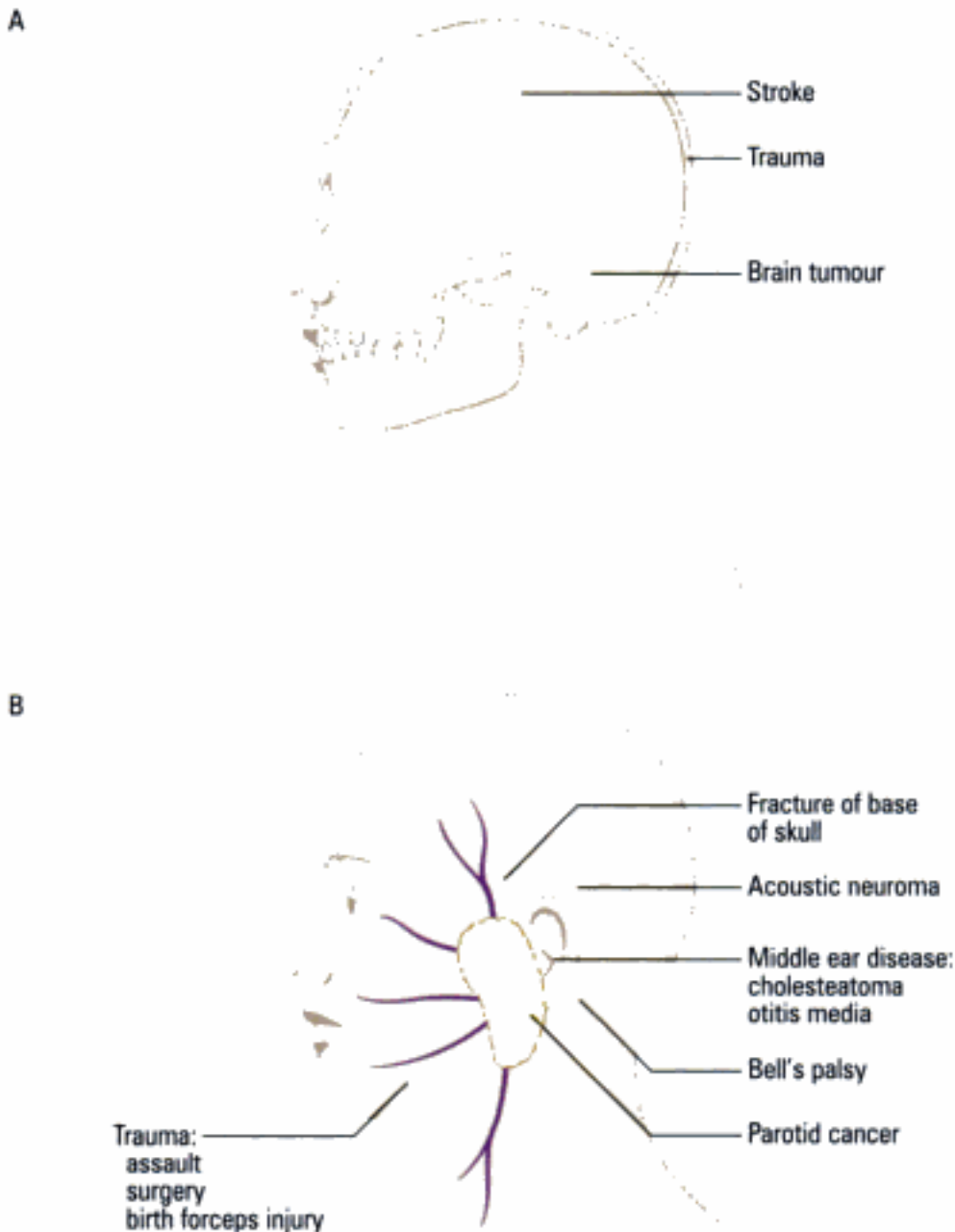


Figure 11.3 Causes of facial palsy: A, upper motor neurone lesions; B, lower motor neurone lesions of the seventh nerve

Table 11.2 Main causes of facial palsy (paralysis)

Upper motor neurone lesion

- Cerebrovascular accident
- Trauma
- Tumour
- Infection
- Multiple sclerosis
- Moebius syndrome

Lower motor neurone lesion

- Systemic infection
- Bell's palsy (herpes simplex virus usually)
- HIV infection
- HTLV-1 infection
- Lyme disease (*Borrelia burgdorferi*)
- Varicella-zoster virus infection ($\pm$ Ramsay-Hunt syndrome)
- Cytomegalovirus, Epstein-Barr virus and influenza viruses

Other

- Kawasaki disease
- Diabetes
- Middle-ear disease:
 - otitis media
 - cholesteatoma
- Lesion of skull base:
 - fracture
 - infection
 - sarcoidosis
- Parotid lesion:
 - tumour
- Trauma to branch of facial nerve
- Barotrauma
- Connective tissue disease
- Sarcoidosis
- Melkersson-Rosenthal syndrome

meningitis

carcinomatosis.

- Bony canal lesions. The level of involvement can be estimated in three ways: (1) below the geniculate ganglion where lacrimation will be spared; (2) below the chorda tympani where taste from the anterior two-thirds of the tongue is spared; or (3) below the nerve to stapedius which, if involved, may give rise to hyperacusis due to fixation of the stapedius muscle. The causes can be:

Ramsay-Hunt syndrome, caused by varicella-zoster virus infection, which allegedly involves the facial nerve at the geniculate ganglion
Bell's palsy can involve the nerve anywhere in the bony stylomastoid canal

fracture of the temporal bones of the skull can involve the nerve anywhere in the bony canal in that bone

haemorrhage may occur into the canal in hypertensive states
leukaemic and other malignant deposits are rare causes.

- Middle-ear conditions, which may be the cause and include:
 - chronic otitis media
 - cholesteatoma
 - ear surgery, especially mastoidectomy.
- Damage caused to the nerve after leaving the stylomastoid canal.

Trauma: use of forceps in delivery, stab wounds and facial lacerations can cause facial paralysis

Parotid lesions: benign tumours in the main displace the facial nerve, but malignant tumours infiltrate the nerve and cause paralysis.

Sarcoidosis of the parotid gland (as part of uveoparotitis) by its diffuse involvement of the gland can cause compression of the nerve.

Leprosy, but this is more common in the upper part of the face and can even be bilateral. It may be possible to palpate the nerve as a cord which can be rolled under the skin.

Acute infective polyneuritis (Guillain-Barré syndrome).

- The common causes of facial paralysis are:

Strokes, seen mainly in older males and usually caused by a cerebrovascular accident.

Bell's palsy, seen mainly in younger patients and thought for many years to be idiopathic. However, it is mainly related to infection and swelling within the confines of the stylomastoid canal, usually due to herpes simplex virus.

Lesions involving the facial nerve (e.g. assault with a knife or bottle, malignant tumours in, or surgery to, the parotid or submandibular region).

Occasionally, a temporary facial palsy follows the (mal-)administration of an inferior alveolar local analgesic, if the anaesthetic diffuses from the pterygomandibular space distally through the parotid gland, when it can reach and temporarily paralyse the facial nerve.

Patterns of facial weakness

Laterality and level are important clinical features.

- Upper motor neurone lesions (supranuclear lesions) will produce lower facial weakness. The weakness does not affect the forehead, which has bilateral cortical representation. The neurological lesion is contralateral to the lower facial weakness. The causes include vascular events such as strokes, tumours and demyelination.
- Lower motor neurone lesions (infranuclear lesions) produce full ipsilateral hemifacial weakness, including the forehead.

Differentiating nuclear from infranuclear lesions depends on the presence of other neurological signs. Contralateral limb weakness suggests a pontine level lesion and therefore a nuclear facial nerve lesion. Cerebellopontine angle lesions typically affect multiple cranial nerves as well as producing hyperacusis and disturbances of lacrimation, taste and salivation.

Lacrimation is affected in a proximal lesion of the facial canal, but is spared in a more distal lesion. Salivation and taste are affected by all

facial canal lesions. Facial level lesions affect only muscle function, leaving lacrimation, salivation and taste intact.

Clinical features

In facial palsy, the patient typically complains of impaired:

- smile
- speech
- ability to whistle.

In addition, on the affected side:

- the forehead is unfurrowed
- the patient is unable to close the eye.
- the eye rolls upward (Bell's sign) on attempted closure
- tears tend to overflow onto the cheek (epiphora)
- the nasolabial fold is obliterated
- the corner of the mouth droops
- saliva may dribble from the commissure
- food collects in the vestibule
- plaque accumulates on the teeth.

Depending on the site of the lesion, other features such as loss of taste may be associated.

Upper motor neurone palsy

The neurones to the upper face receive bilateral UMN innervation. UMN facial palsy is usually caused by damage in the middle capsule of the brain. Damage thus extends to include hemiplegia and sometimes affects speech, but extrapyramidal influences remain and thus there can still be involuntary facial movements, for example, on laughing because of the bilateral cortical representation. A UMN lesion, therefore, is characterised by:

- contralateral facial palsy
- some sparing of the frontalis and orbicularis oculi muscles
- facial movements with emotional responses.

There may also be on the side of facial palsy:

- paresis of the arm (monoparesis)
- paresis of the arm and leg (hemiparesis)
- aphasia.

Lower motor neurone palsy

In contrast, LMN facial palsy is characterised by:

- total unilateral paralysis of all muscles of facial expression
- absence of voluntary and emotional facial responses
- no hemiparesis.

Diagnosis

The history should be directed to elicit features suggestive of stroke, trauma, including underwater diving (barotrauma), camping or walking in areas that may contain ticks (Lyme disease), the possibility of HIV infection and, in Afro-Caribbeans, the possibility of HTLV-1 infection. A facial paresis which is slowly evolving, associated with other focal neurology, facial twitching, multiple cranial nerve deficits or with chronic Eustachian tube dysfunction suggests a possible malignant cause. A neck or parotid mass or history of previous head or neck malignancy is suspicious (Fig. 11.4).

The examination should include:

- Ear and mouth examination to exclude Ramsay-Hunt syndrome (herpes zoster of the facial nerve ganglion which causes lesions in the palate and ipsilateral ear, and facial palsy).
- Ear examination to look for discharge and other signs of middle-ear disease.

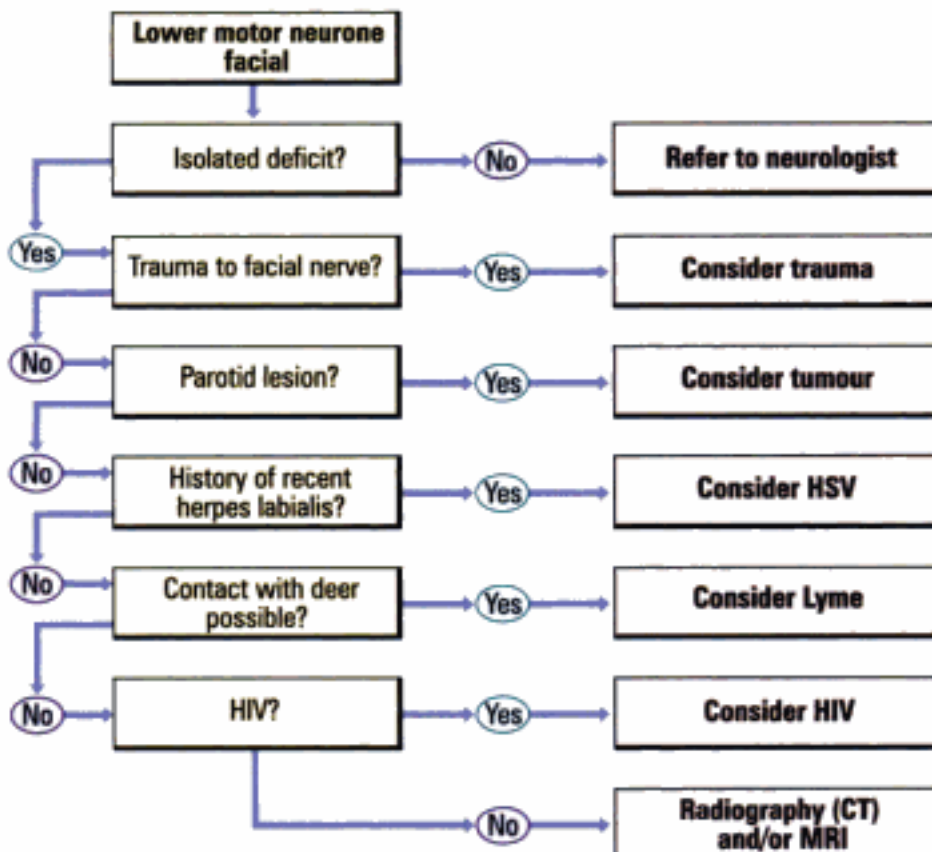


Figure 11.4 Algorithm for LMN facial palsy

- A full neurological examination, especially to exclude lesions of other cranial nerves and to exclude a stroke. The facial nerve weakness is demonstrated by asking the patient to:
 - close the eyes against resistance
 - raise the eyebrows
 - raise the lips to show the teeth
 - try to whistle.
- A test for loss of hearing should be carried out.
- A test for taste loss should be carried out.

Investigations which may be indicated include:

- Imaging with CT/MRI, and chest and skull radiography to look particularly for central lesions.
- A study of evoked potentials to assess the degree of nerve damage. Facial nerve stimulation or needle electromyography may be useful, as may electrogustometry.
- Blood pressure measurement should be carried out to exclude hypertension.
- Fasting blood sugar levels should be tested to exclude diabetes.
- In some areas, Lyme disease (tick-borne infection with *Borrelia burgdorferi*) should be excluded by enzyme-linked immunosorbent assay (ELISA).
- Tests for other virus infections, such as HIV or HTLV-1, may need to be considered.
- Serum angiotensin converting enzyme (ACE) levels to exclude sarcoidosis.
- Lumbar puncture is needed occasionally.

Management

Management is of the underlying condition. Most patients with Bell's palsy are otherwise healthy and present no other management difficulties, but there are occasional (possibly coincidental) associations with diabetes mellitus, hypertension and lymphoma.

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Soreness and Ulcers

KEY POINTS

Main causes of mouth ulcers

- Local causes
- Recurrent aphthae
- Malignant neoplasms
- Drugs
- Systemic disease:
 - microbial disease
 - mucocutaneous disease
 - blood disorders
 - gastrointestinal disease
 - rheumatic diseases
 - vasculitides
 - endocrine
- Disorders of uncertain pathogenesis

Introduction

The mouth can be sore for a number of reasons, especially where there are distinct conditions such as:

- Dry mouth – which predisposes to soreness, since the lubricating and protective functions of saliva are reduced and infections such as candidiasis are more common.
- Epithelial thinning or breaches can also result in soreness. This occurs in:

Mucosal inflammation: any inflammatory lesion can cause soreness; candidiasis is one example (antibiotic sore tongue).

Mucosal atrophy: this is the term often used for thinning of the epithelium, which has a red appearance since the underlying lamina propria shows through. Most commonly seen in geographic tongue (erythema migrans, benign migratory glossitis), atrophy may also be seen in lichen planus or systemic disorders such as deficiency states (of iron, folic acid or B vitamins).

Mucosal erosions: this is the term used for superficial breaches of the epithelium which often initially have a red appearance, since there is little damage to the underlying lamina propria. If a breach penetrates the full thickness of the epithelium, however, it typically becomes covered by a fibrinous exudate and then has a yellowish appearance. Erosions are common in lichen planus.

Mucosal ulcers: this is the term used usually where there is damage to both epithelium and lamina propria, and then a crater forms, sometimes made more obvious clinically by oedema or proliferation causing swelling of the surrounding tissue (Fig. 12.1). An inflammatory halo if present, also highlights the ulcer with a red halo, around the yellow or grey ulcer. Ulcers are common in recurrent aphthous stomatitis. Most ulcers/erosions are due to local causes such as trauma or burns, but neoplasms and systemic disorders must always be considered.

- Dry mouth and epithelial thinning can result from irradiation of the oral region.

Soreness may also be encountered in an apparently normal mouth with no clinical signs of any of the above. This can be due to:



Figure 12.1 Ulceration in acute necrotising gingivitis destroys the interdental papillae particularly

- subclinical disease, such as a deficiency state, particularly of vitamin B₁₂, or even anaemia
- psychogenic causes, which can underlie a sore tongue or sore mouth (often described as a burning sensation) – sometimes known as oral dysaesthesia
- neuropathies, such as in diabetes mellitus.

Ulcers

- Ulcers and erosions can be the final common manifestation of a spectrum of conditions ranging from epithelial damage resulting from an immunological attack – as in pemphigus, pemphigoid, lichen planus – to damage because of an immune defect as in HIV disease and leukaemia, infections as in herpesviruses, tuberculosis and syphilis, or nutritional defects such as in vitamin deficiencies and some intestinal disease (Table 12.1).
- The most important feature of ulceration is whether the ulcer is persistent, since this may indicate that the ulcer is caused by:
 - neoplasia such as carcinoma
 - chronic trauma
 - a chronic skin disease such as pemphigus
 - a chronic infection such as syphilis, tuberculosis or mycosis.
- An important feature is whether one or more than one ulcer is present, since malignant tumours usually cause a single lesion.
- A single ulcer persisting for more than 3 weeks without signs of obvious healing must be taken seriously, as it could be a neoplasm.
- Multiple persistent ulcers are mainly caused by:
 - skin diseases, such as pemphigus, pemphigoid or lichen planus
 - gastrointestinal disease
 - immune defect.
- Multiple non-persistent ulcers can be caused by aphthae, when the ulcers heal spontaneously, usually within 1 week to 1 month. If this is not the case, an alternative diagnosis should be considered.
- Erosions or ulcers on both sides at the commissures of the lips are usually angular stomatitis (cheilitis), but sores are also sometimes caused at the angles by trauma (such as dental treatment) or infection (such as recurrent herpes labialis).

Ulcers of local causes

- At any age there may be factitious ulceration, especially of the maxillary gingivae, or burns with chemicals of various kinds, heat, cold, or ionising radiation.

Table 12.1 Main causes of mouth ulcers**Local causes**

- Trauma:
 - sharp teeth or restorations
 - appliances
 - non-accidental injury
 - self-inflicted
 - iatrogenic
- Burns:
 - heat
 - cold
 - chemical
 - radiation
 - electric
- Recurrent aphthae (and Behçet syndrome)
- Malignant neoplasms:
 - oral
 - encroaching from antrum or nose

Drugs

- Cytotoxics
- NSAIDs
- Nicorandil
- Many others

Systemic disease

- Microbial disease:
 - herpetic stomatitis
 - chickenpox
 - hand, foot and mouth disease
 - herpangina
 - infectious mononucleosis
 - HIV
 - acute necrotising gingivitis
 - tuberculosis
 - syphilis
 - histoplasmosis
 - cryptococcosis
 - blastomycosis
 - paracoccidioidomycosis
 - leishmaniasis

Systemic disease – Contd

- Mucocutaneous disease:
 - lichen planus
 - pemphigus vulgaris
 - pemphigoid and variants
 - erythema multiforme
 - dermatitis herpetiformis
 - linear IgA disease
 - epidermolysis bullosa
 - chronic ulcerative stomatitis
 - other dermatoses
- Blood disorders:
 - anaemia
 - leukaemia
 - myelodysplastic syndrome
 - neutropenia
 - other white cell dyscrasias
 - gammopathies
 - haematinic deficiencies
- Gastrointestinal disease:
 - coeliac disease
 - Crohn's disease
 - ulcerative colitis
- Rheumatic diseases:
 - lupus erythematosus
 - Sweet syndrome
 - Reiter syndrome
- Vasculitides:
 - Behçet syndrome
 - Wegener's granulomatosis
 - periarteritis nodosa
 - giant cell arteritis
- Endocrine disorders:
 - diabetes
 - glucagonoma
- Disorders of uncertain pathogenesis:
 - eosinophilic ulcer
 - hypereosinophilic syndrome
 - necrotising sialometaplasia

- In children they are usually caused by accidental biting, or following dental treatment or other trauma, hard foods or appliance. In child

abuse (non-accidental injury), ulceration of the upper labial fraenum may follow a traumatic fraenal tear. Bruised and swollen lips, and even subluxed teeth or fractured mandible, can be other features of child abuse. The lingual fraenum may be traumatised by repeated rubbing

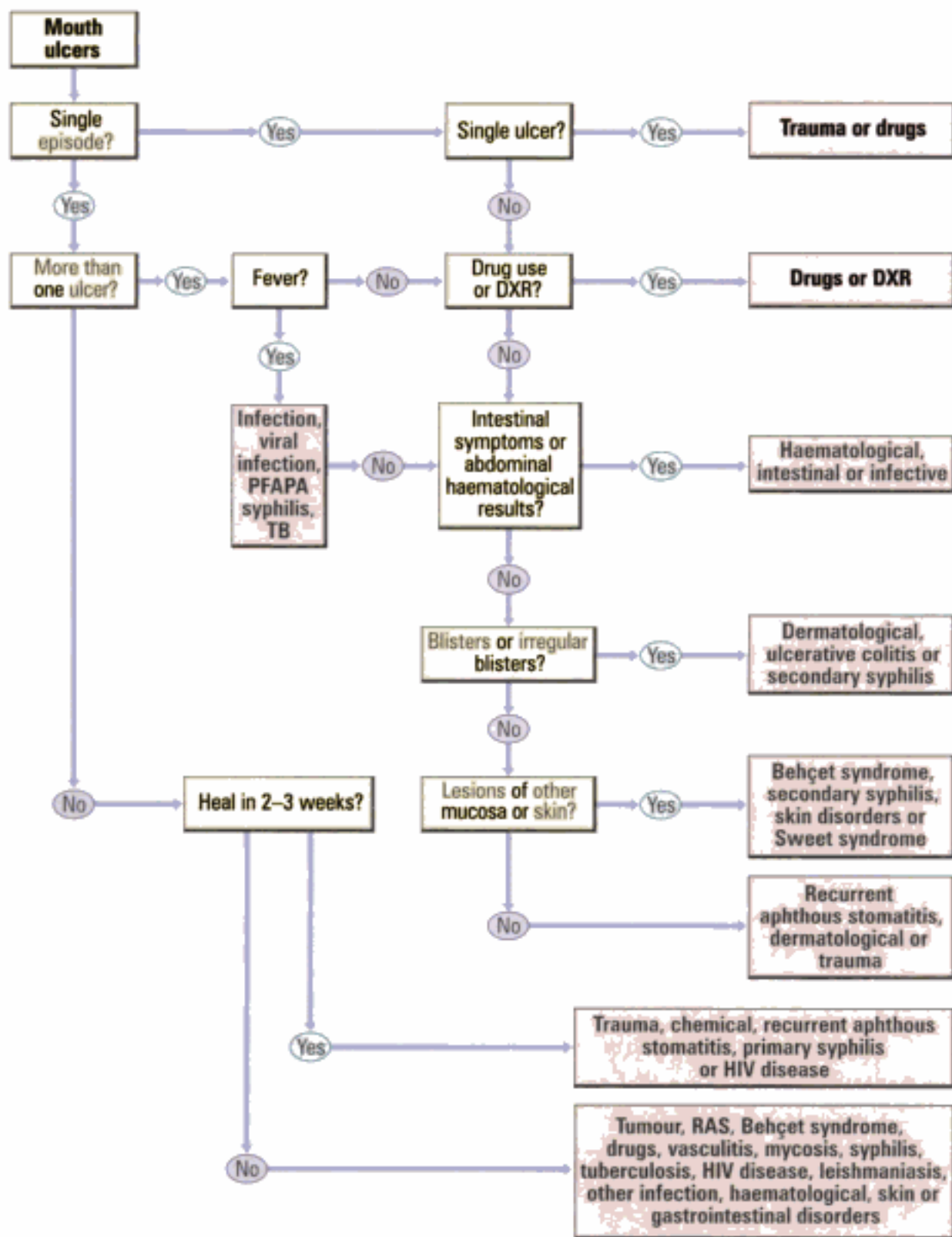


Figure 12.2 Algorithm for oral ulceration. (DXR, irradiation; PFAPA, periodic fever, aphthae, pharyngitis, adenitis; RAS, recurrent aphthous stomatitis; TB, tuberculosis)

over the lower incisor teeth in children with recurrent bouts of coughing as in whooping cough (termed Riga-Fedes disease) or in self-mutilating conditions. Chronic trauma may produce an ulcer with a keratotic margin.

- Trauma can produce ulceration in adults. Sometimes the lingual fraenum is damaged by trauma in cunnilingus, or the palate in fellatio.

Recurrent aphthous stomatitis

Ulcers are commonly aphthae, usually in persons who are otherwise well. Occasionally they are associated with haematinic deficiencies, or are part of Behçet syndrome (see Ch. 15) or PFAPA (see p. 179).

Malignant ulcers

A range of neoplasms may present with ulcers, most commonly these are carcinomas but Kaposi sarcoma, lymphomas and other neoplasms may be seen (see Ch. 20).

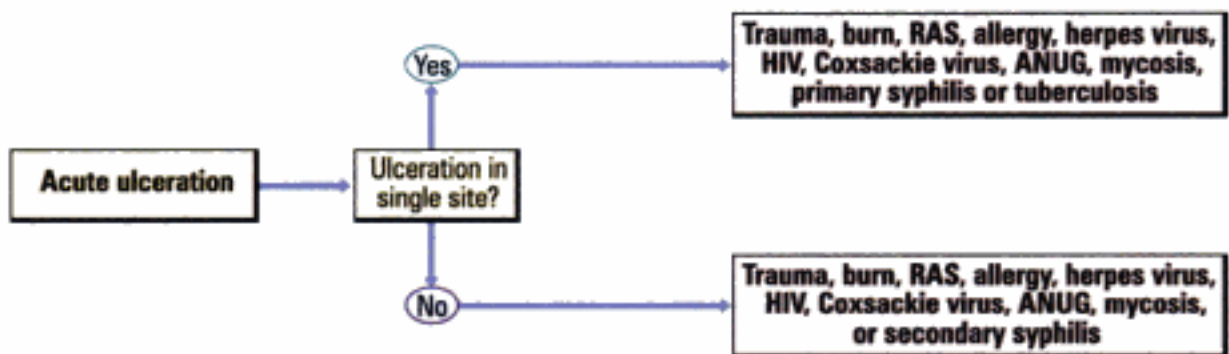


Figure 12.3 Algorithm for acute ulceration

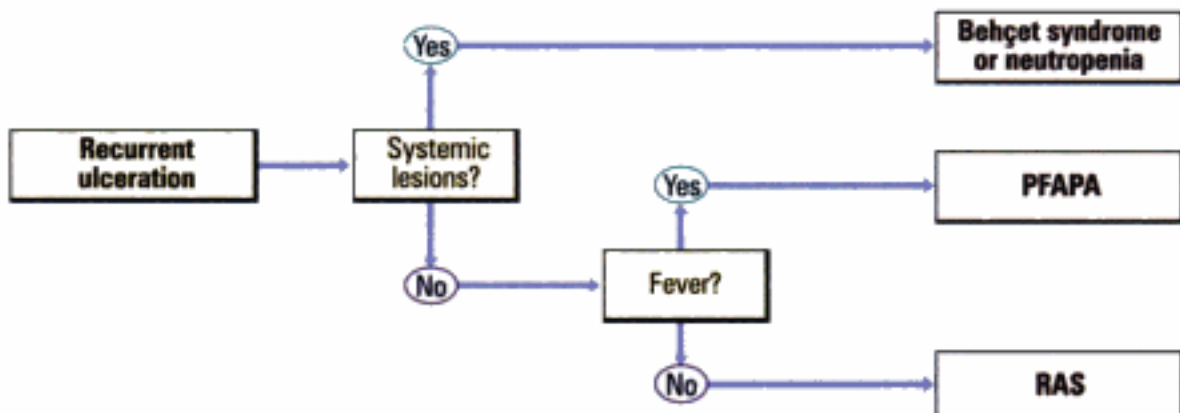


Figure 12.4 Algorithm for recurrent ulcers

Drug-induced ulceration

Drugs may induce ulcers by producing a local burn or by a variety of mechanisms. Cytotoxic drugs (e.g. methotrexate), non-steroidal anti-inflammatory drugs (NSAIDs), alendronate and nicorandil (a potassium channel activator used in cardiac disorders) may be the cause.

Systemic disease

A wide range of systemic diseases, especially infections, blood, gut and skin disorders, may cause oral lesions which, because of the moisture, trauma and infection in the mouth, tend to break down to leave ulcers or erosions (Table 12.2).

- Infective causes of mouth ulcers include mainly viral infections, especially the herpesviruses. Other viruses that may cause mouth ulcers include Coxsackie, echo and HIV viruses. Bacterial causes of mouth ulcers are less common, apart from acute necrotising (ulcerative) gingivitis. Syphilis, either the primary or secondary stages, and tuberculosis are uncommon in the developed world at present but are increasing, especially in HIV/AIDS. Fungal causes of ulcers are also uncommon in the developed world but are increasingly seen in immunocompromised persons and travellers. Protozoal causes of ulcers, such as leishmaniasis, are rare in the developed world but are appearing in HIV/AIDS.

Table 12.2 Infectious diseases which may produce oral ulceration

Disease	Causal agent	Major manifestations
AIDS (HIV infection)	HIV	Pneumonia, Kaposi sarcoma, lymphomas, general lymphadenopathy, candidiasis, herpes simplex virus, hairy leukoplakia, periodontal disease, ulcers, cervical lymph node enlargement
Chickenpox (varicella)*	VZV	Rash evolves through macule, papule, vesicle and pustule; rash crops and is most dense on trunk. General lymphadenopathy, oral ulcers, cervical lymph node enlargement
Cytomegalovirus*	CMV	Glandular-fever-type syndrome (Paul-Bunell negative), general lymphadenopathy
Gonorrhoea	<i>Neisseria gonorrhoea</i>	Urethritis, pharyngitis

Contd

Table 12.2 Contd

Disease	Causal agent	Major manifestations
Hand, foot and mouth disease	Coxsackie viruses	Rash, minor malaise, oral ulceration (usually mild)
Herpangina	Coxsackie viruses	Fever, sore throat, vesicles and ulcers on soft palate, cervical lymph node enlargement
Herpes simplex*	HSV	Fever, oral ulceration, gingivitis, gingivostomatitis, herpes labialis (secondary infection), cervical lymph node enlargement
Herpes zoster* (shingles)	VZV	Rash like chickenpox but limited to dermatome. Severe pain. Oral ulceration in zoster of maxillary or mandibular division of trigeminal nerve. Ulcers on palate and in pinna of ear in Ramsay–Hunt syndrome
Infectious mononucleosis	EBV	Fever, pharyngitis, general lymphadenopathy, tonsillar exudate, palatal petechiae, oral ulceration
Mucocutaneous lymph node syndrome (Kawasaki disease)	?	Rash, hands and feet desquamation, general lymphadenopathy, myocarditis, strawberry tongue, labial oedema, pharyngitis
Mycoplasmal pneumonia (atypical pneumonia)	Mycoplasma	Sore throat, fever, pneumonia, erythema multiforme occasionally
Pertussis [†] (whooping cough)	<i>Bordetella pertussis</i>	Cough, fever, occasionally ulceration of lingual fraenum
Syphilis	<i>Treponema pallidum</i>	Chancres, lymphadenopathy, rash, ulceration, mucous patches
Toxoplasmosis*	<i>Toxoplasma gondii</i>	Glandular-fever-type syndrome (Paul–Bunell negative), general lymphadenopathy, cough, sore throat
Tuberculosis*	<i>Mycobacterium tuberculosis</i>	Ulceration, fever, weight loss, general lymphadenopathy

AIDS, acquired immune deficiency syndrome

*Prevalent and often widespread infections in the immunocompromised, high-risk patients such as renal transplant or leukaemic patients

[†]Some cases are caused by *Bordetella parapertussis* or by viruses

- Skin (mucocutaneous) disorders that may cause oral erosions or ulceration (or occasionally blisters) include particularly lichen planus, occasionally pemphigoid, and rarely pemphigus and erythema multiforme.
- Haematological disease can cause ulcers. Mouth ulcers may be seen in leukaemias, associated with cytotoxic therapy, with viral, bacterial or fungal infection, or be non-specific. Other oral features may include purpura, gingival bleeding, lymphadenopathy, recurrent herpes labialis and candidiasis.
- Gastrointestinal disorders may result in soreness or mouth ulcers. Some patients with aphthae have intestinal disease, such as coeliac disease, causing malabsorption and deficiencies of haematinics, when they may also develop angular stomatitis or glossitis. Crohn's disease and pyostomatitis vegetans may cause ulcers. Orofacial granulomatosis (OFG), which has many features reminiscent of Crohn's disease, may also cause ulceration.
- Rheumatic diseases may cause ulcers which may be seen in lupus erythematosus, rheumatoid disease and Reiter syndrome.

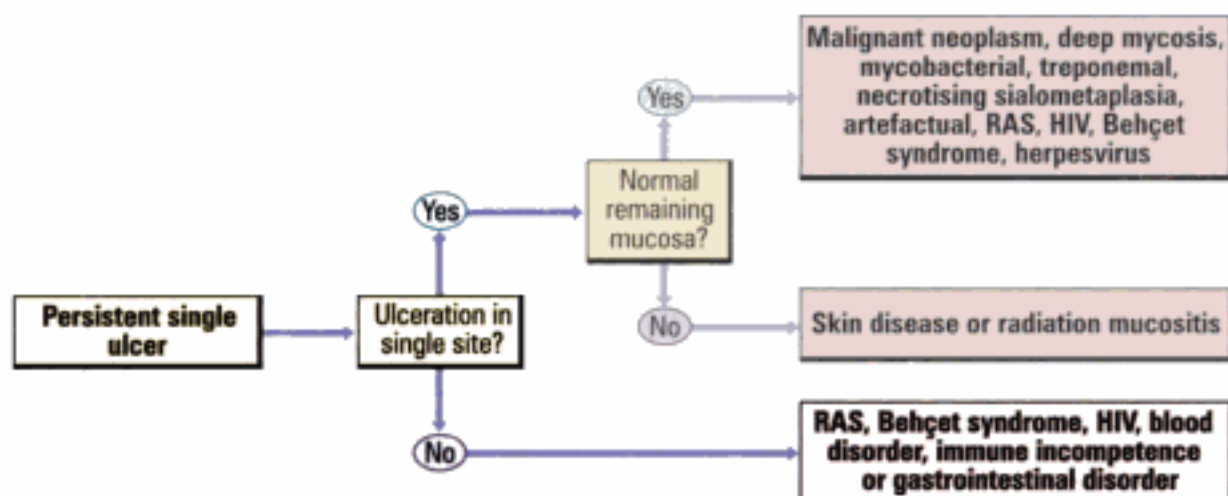


Figure 12.5 Algorithm for persistent single ulcers

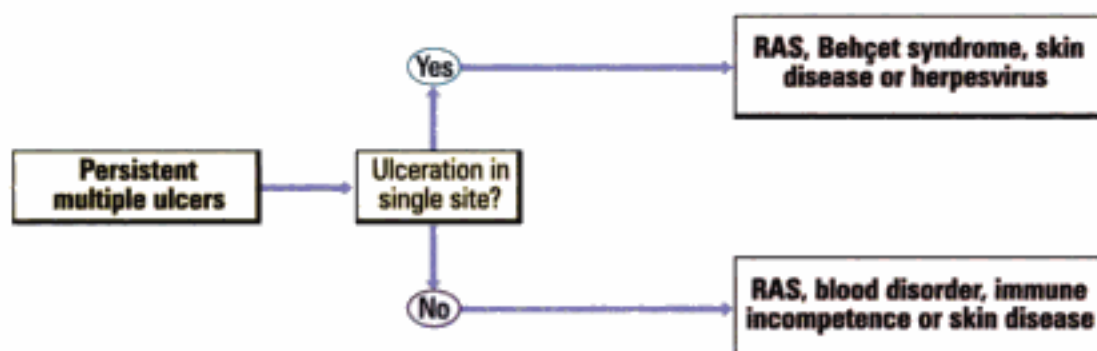


Figure 12.6 Algorithm for persistent multiple ulcers

- Vasculitides may cause ulcers, which may be seen in Behçet syndrome, pyoderma gangrenosum, Wegener's granulomatosis and giant cell arteritis.
- Ulcers may occasionally have an endocrine cause. Diabetes may be complicated by mouth ulceration.
- Ulcers may also in disorders whose pathogenesis is uncertain. Ulcers may be seen in necrotising sialometaplasia (see Ch. 37), sarcoidosis, periodic fever, aphthae, pharyngitis and adenitis (PFAPA) (see Ch. 37) and hypereosinophilic syndrome.

Diagnosis

Making a diagnosis of the cause for oral soreness or ulceration is based mainly on the history and clinical features. The number, persistence, shape, character of the edge of the ulcer and the appearance of the ulcer base should also be noted. Ulcers should always be examined for induration (firmness on palpation), which may be indicative of malignancy. Unless the cause is undoubtedly local, general physical examination is also indicated, looking especially for mucocutaneous lesions, lymphadenopathy or fever (Figs. 12.2–12.7).

Features that might suggest a systemic background to mouth ulcers include:

- extraoral features such as:
 - skin lesions
 - ocular lesions
 - anogenital lesions
 - purpura
 - fever
 - lymphadenopathy
 - hepatomegaly

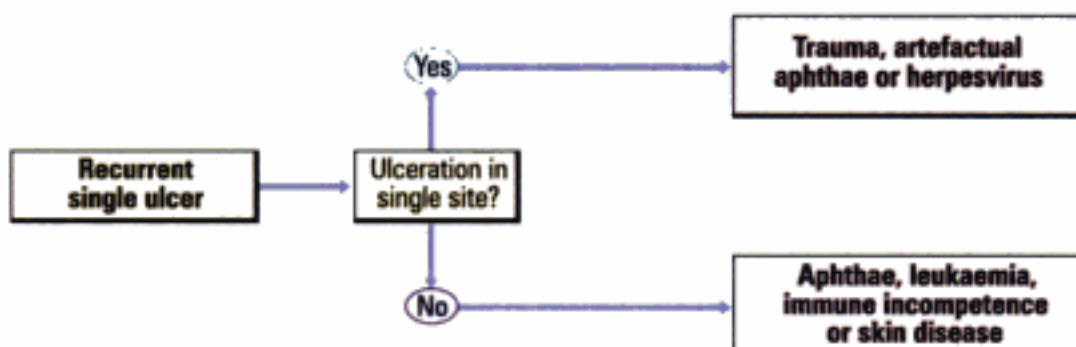


Figure 12.7 Algorithm for recurrent single ulcers

splenomegaly

chronic cough

gastrointestinal complaints (e.g. pain, altered bowel habits, blood in faeces)

loss of weight or, in children, a failure to thrive
weakness

- an atypical history or ulcer behaviour such as:
 - onset of ulcers in later adult life
 - exacerbation of ulcers
 - severe aphthae
 - aphthae unresponsive to topical hydrocortisone or triamcinolone
- other oral lesions, especially:
 - candidiasis
 - herpetic lesions
 - glossitis
 - petechiae
 - gingival bleeding
 - gingival swelling
 - necrotising gingivitis or periodontitis
 - hairy leukoplakia
 - Kaposi sarcoma.

Investigations

Investigations which may sometimes be indicated include:

- Blood tests – may be useful for excluding possible deficiencies or other conditions when a systemic cause, such as leukaemia or HIV infection, is suspected.
- Microbiological and serological investigations – may be needed, especially if microbial causes are suspected.
- Glucose assays (urine and blood) – may occasionally be needed to exclude diabetes.
- Biopsy – may be needed, especially where there:
 - is a single ulcer persisting for more than 3 weeks
 - is an ulcer which appears traumatic in aetiology but which persists for more than 3 weeks after relief from the trauma
 - is induration
 - are skin lesions
 - are lesions in other mucosae
 - are other related systemic lesions, signs or symptoms.
- Imaging, such as radiography and other special investigations – may be indicated where there are possible lesions such as tuberculosis, the deep mycoses, carcinoma or sarcoidosis.

Management

- Treat the underlying cause.
- Remove aetiological factors.
- Ensure any possible traumatic element is removed (e.g. a denture flange).
- Prescribe a chlorhexidine 0.2% aqueous mouthwash.
- Maintain good oral hygiene.
- A benzydamine mouthwash or spray may help ease discomfort.
- Topical corticosteroids are useful in the management of many oral ulcerative conditions where there is no systemic involvement, such as recurrent aphthous stomatitis and oral lichen planus (see Table 12.1).
- Creams, gels and inhalers are better than ointments since the latter adhere poorly to the mucosa. However, creams can be bitter and gels can irritate.
- Patients should not eat or drink for 30 minutes after using the steroid, in order to prolong contact with the lesion.
- Adverse effects are important mainly with systemic steroids. With many topical steroids there is little systemic absorption and thus no significant adrenocortical suppression. In patients using potent topical steroids for more than a month it is prudent to add an antifungal, since candidiasis may arise.

Other topical immunomodulatory agents

Topical immunosuppressants, such as tacrolimus, can be:

- effective in ulcerative disorders
- more effective if used along with topical corticosteroids
- expensive
- associated with adverse effects only rarely.

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SECTION III

PDFREE COMUNIDAD ODONTOLOGICA

Common and Important Oral Conditions

13

PDFREE COMUNIDAD ODONTOLOGICA

Angioedema (Angioneurotic Oedema)

Introduction

The lips can swell (Fig. 13.1) in either allergic angioedema (a type 1 hypersensitivity response seen mainly in those with an atopic tendency) or hereditary angioneurotic oedema (HANE; caused by a deficiency of the complement component C1 esterase inhibitor). These manifest with oral or facial swelling of acute onset with rapid development of oedematous swelling of the lip(s) and tongue. The danger is that oedema may also involve the neck and hazard the airway.



Figure 13.1 Lip swelling in angioedema

Allergic angioedema

Incidence

It is common, far more common than HANE.

Age

It occurs mainly in adults.

Sex

It is most prevalent in females.

Geographic

No known geographic incidence.

Aetiology

Allergic angioedema is a type 1 reaction which may be induced by:

- Foods: nuts are a well-known cause.
- Drugs:
 - antibiotics
 - others.
- Other allergens.

Clinical features

- The facial oedema can cause pronounced labial and periorbital swelling, but when oedema involves the tongue and neck and extends to the larynx, it can cause rapidly fatal respiratory obstruction.
- Acute allergic oedema of this type can develop alone or may be associated with anaphylactic reactions (and/or urticaria).
- Angioedema is characterised by the transient nature of the swelling and the lack of scaling.

Diagnosis

Angioedema is diagnosed clinically and from a history of atopic disease and/or exposure to allergen, and sometimes by allergy testing (prick test).

Management

Although the swelling is of acute onset and often only mild and transient, there is always the potential of obstruction of the airway, and thus urgent treatment is indicated.

- In severe cases, especially if there is any potential or real threat to the airway, the emergency should be managed with intramuscular adrenaline (epinephrine), and with systemic corticosteroids or antihistamines as for an anaphylactic reaction.
- Mild angioedema may respond to antihistamines, such as chlorpheniramine, or to a sympathomimetic agent such as ephedrine by mouth.
- For rare intractable chronic cases, corticosteroids may be required.

Drug-induced non-allergic angioedema

Non-allergic oral swelling can arise in response to angiotensin converting enzyme (ACE) inhibitor therapy due to a rise in levels of bradykinins and/or altered levels or function of C1 esterase inhibitor. The swelling usually affects the lips, although it can be localised to the tongue, and is occasionally fatal. Black people may be at particular risk of this adverse drug reaction.

Hereditary angioedema (C1 esterase inhibitor deficiency)

HANE mimics allergic angioedema, though it produces a more severe reaction. Despite its hereditary nature, usually as an autosomal dominant trait, the disease may not present until later childhood or adolescence, and nearly 20% of cases are caused by spontaneous mutation.

Incidence

It is uncommon.

Age

It can occur at any age.

Sex

It occurs equally in both sexes.

Geographic

No known geographic incidence.

Predisposing factors

A genetically determined deficiency of an inhibitor of the enzyme C1 esterase leads to continued complement activation after trauma, and acti-

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vation of kinin-like substances which cause a sudden increase in capillary permeability. The C4 is consumed and its plasma level falls, but the level of C3 is usually normal.

Clinical features

- Blunt injury is the most consistent precipitating event. The trauma of dental treatment is a potent trigger, and some attacks follow emotional stress.
- Abdominal pain, nausea or vomiting, diarrhoea, rashes and peripheral oedema sometimes herald an attack.
- HANE typically produces acute onset of oedema affecting the lips, tongue, mouth, face and neck region, the extremities and the gastrointestinal tract after minor trauma.
- Oedema may persist for many hours and even up to 4 days and, throughout, involvement of the airway is a constant threat.
- The mortality may be as high as 30% in some families, but the disease is compatible with prolonged survival if emergencies are avoided or effectively treated.

Diagnosis

Diagnosis of hereditary angioedema is from:

- Family history.
- Clinical features with a history of oedema after trauma.
- Blood tests; low C4, but normal C3 levels, and absence of C1 esterase inhibitor activity. In 85% of cases C1 esterase levels are reduced (type 1 HANE) but in 15% the enzyme is present but dysfunctional (type 2 HANE).

Management

Management is with inhibitor replacement, fresh plasma, plasminogen inhibitors, such as tranexamic acid, or androgenic steroids, such as danazol or stanazolol.

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14

PDFFREE COMUNIDAD ODONTOLOGICA

Angular Cheilitis (Angular Stomatitis)

Introduction

Angular cheilitis is inflammation at the commissures (angles) of the lips (Fig. 14.1).

Incidence

Angular cheilitis is common.

Age

It occurs mostly in adults.

Sex

It occurs in both sexes.

Geographic

No known geographic incidence.

Predisposing factors

Angular stomatitis is predisposed by what are known as the '3Ds'.

- Denture-wearing and disorders that predispose to candidiasis:
 - dry mouth
 - tobacco smoking.
- Deficiency states such as:
 - iron deficiency
 - hypovitaminoses (especially B)

- malabsorption states (e.g. Crohn's disease) possibly zinc deficiency, but only rarely
- defects in immunity such as in Down syndrome, HIV infection, diabetes, cancer and others.
- Disorders where the lips are enlarged, such as orofacial granulomatosis, Crohn's disease and Down syndrome.

Aetiology

A number of factors (infective, mechanical, nutritional or immunological) may be implicated alone or in combination. Angular cheilitis is most often chronic, seen in the elderly, and due to infective and/or mechanical causes. *Candida albicans* and *Staphylococcus aureus* are often isolated from the lesions.

- Infective agents are probably the major cause. Infective agents can be isolated in up to 54% of lesions, with mainly *Candida* or staphylococci being isolated.
 - *Candida albicans* is the most commonly isolated and is typically carried in the saliva. Oral candidiasis causing cheilitis is particularly common in those wearing dentures, especially where there is denture-related stomatitis, and was probably responsible for some cases of cheilitis attributed to allergy to denture materials – since contamination of denture-material by *Candida* may cause false-positive patch-test reactions. Dry mouth also predisposes to candidiasis.
 - *Staphylococcus aureus* and/or streptococci may also be cultured from lesions, and may be harboured in the nose (anterior nares).
- Mechanical factors may play a part in the edentulous patient who does not wear, or who has inadequate, dentures. As a consequence of ageing,



Figure 14.1 Angular stomatitis

the upper lip overhangs the lower at the angles of the mouth, producing a fold that keeps a small area of skin macerated. Maceration of the commissural epithelium can also be brought about by habitual licking as a nervous tic, or by sucking on objects (perleche). Few authors consider that the lesion results solely from maceration.

- Deficiencies of haematinics (factors required for blood formation – which include iron, vitamin B and folic acid) and deficiencies of immunity can lead to proliferation of *Candida* species.
 - Nutritional deficiencies, in particular deficiencies of riboflavin, folate, iron, zinc and general protein malnutrition, have been incriminated in angular stomatitis but are rare. Angular stomatitis is, very occasionally, an isolated initial sign of anaemia or vitamin deficiency, such as vitamin B₁₂ deficiency; more often there is also oral ulceration and glossitis.
 - Immune deficiency such as in diabetes, Down syndrome or HIV disease may result in angular cheilitis associated with candidiasis.
- In uncommon conditions where the lips are enlarged, such as orofacial granulomatosis, up to 20% of individuals have angular stomatitis, although *Candida* species are not often isolated.

Clinical features

- Soreness, erythema and fissuring affect the angles of the mouth symmetrically. Angular cheilitis most commonly presents as roughly triangular areas of erythema and oedema at both commissures. Atrophy, erythema, ulceration, crusting, and scaling may be seen. Recurrent exudation and are frequent. An eczematous dermatitis may extend some distance onto the cheek or chin as an infective eczematoid reaction or as a reaction to topical medicaments. In long-standing lesions, suppuration and granulation tissue may develop. Lesions occasionally extend beyond the vermilion border onto the skin in the form of linear furrows or fissures radiating from the angle of the mouth (rhagades), mainly in the more severe forms, especially in denture wearers.
- Commonly, there is also associated denture-related stomatitis.
- Rarely, there is also commissural leukoplakia intraorally.

Diagnosis

- This is usually a clinical diagnosis, made by clinical examination alone. Inspection may reveal palatal erythema caused by associated denture-related stomatitis, usually due to candidiasis. An underlying nutritional deficiency may be revealed by a depapillated tongue in iron deficiency, a depapillated glossy red tongue in folate deficiency or a reddish-purple depapillated tongue in vitamin B deficiency. Angular cheilitis

accompanied by alopecia, diarrhoea and non-specific oral ulcerations, most commonly of the tongue and buccal mucosa, may suggest zinc deficiency.

- In all cases in denture wearers, *Candida* should be sought not only in the lesions but also beneath the denture. Microbial cultures and a haematological workup (blood picture, and assays of levels of serum iron/ferritin, serum vitamin B₁₂ and corrected red blood cell folate) are indicated when systemic involvement is suspected.

Management

Management of angular cheilitis is sometimes difficult and may need to be prolonged.

- Tobacco habits should be stopped.
- Eliminate any underlying systemic predisposing factors. Underlying systemic disease must be sought and treated, and a course of oral iron and vitamin B supplements may be helpful in indolent cases.
- If infection is the cause of angular cheilitis, treatment will only be effective if the underlying disease process is also being treated.
- The skin lesions should be swabbed.
- Permanent cure can be achieved only by eliminating candidiasis as well as the growth of *Candida* beneath the denture. Recurrence of angular cheilitis must be prevented by eliminating organisms from their reservoir. Dentures harbour *Candida* and require proper disinfection. Dentures should be kept out of the mouth at night and stored in a candidacidal solution such as hypochlorite. Denture-related stomatitis should be treated with an antifungal. Miconazole may be preferable (cream applied locally, together with the oral gel) as it has some Gram-positive bacteriostatic action, but there is a high relapse rate unless treatment is prolonged. Miconazole is absorbed systemically and may occasionally potentiate the action of warfarin, phenytoin and the sulphonylureas. Nystatin or amphotericin (as cream or ointment) should therefore be tried first in patients taking these drugs. Angular stomatitis should be treated with a topical antifungal (e.g. miconazole).
- *Staphylococcus* infection can be cleared with topical antibiotics such as fusidic acid ointment or cream used at least four times daily.
- Mixed infections of *Candida* and *Staphylococcus* respond best to topical miconazole.
- Mechanical predisposing factors should be corrected. A change in dentures may be necessary; new dentures which restore facial contour may help.
- In rare intractable cases, surgery or, occasionally, collagen injections may be useful in trying to restore normal commissural anatomy.

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Aphthae (Aphthous Stomatitis)

Introduction

Recurrent aphthous stomatitis (RAS), also known as aphthae or canker sores, is a common condition which is characterised by presenting typically:

- with multiple recurrent small, round or ovoid ulcers which have circumscribed margins, erythematous haloes, and yellow or grey floors
- on non-keratinised and mobile mucosae – they are rare on gingivae or palate
- first in childhood or adolescence

It is important to note that individual aphthae last only a limited period of time, before they heal: this is quite a different history from ulcers that persist without healing, such as malignant ulcers.

Incidence

RAS affects at least 10% of the population, and the highest prevalence, up to 25%, is in higher socio-economic classes.

Age

RAS typically starts in childhood or adolescence.

Sex

There is a slight female predisposition to RAS.

Geographic

RAS occurs worldwide though it appears most common in the developed world.

Predisposing factors

- A genetic predisposition is present, as shown by an increased frequency of HLA types HLA-A2, A11, B12 and DR2 in RAS patients, and a positive family history in about one-third of patients with RAS.
- Haematinic deficiency is found in up to 20% of patients (deficiencies of iron, folic acid (folate) or vitamin B). Iron deficiency is usually due to chronic haemorrhage (e.g. from the gastrointestinal or genitourinary tract); deficiencies of folate may be dietary, or related to malabsorption or drugs. Folic acid is found in green leafy vegetables especially, and body stores are small; anticonvulsants (including carbamazepine), alcohol and some cytotoxic drugs can produce folate deficiency. Deficiencies of vitamin B, such as B₁₂, may be dietary, related to malabsorption, or drugs. Vitamin B₁₂ is found especially in meat, and dietary deficiency can arise particularly in vegans, despite the fact that body stores in the liver can last about 3 years. Absorption in the ileum requires intrinsic factor, which is lacking in pernicious anaemia, and after gastrectomy. Histamine H₂ receptor antagonists (cimetidine, ranitidine, omeprazole) can also impede vitamin B₁₂ absorption.
- Malabsorption in gastrointestinal disorders; in about 3% of patients with RAS, coeliac disease (gluten-sensitive enteropathy), but also occasionally Crohn's disease, pernicious anaemia and dermatitis herpetiformis may be seen.
- Cessation of smoking; may precipitate or exacerbate RAS in some cases, but the reason is unclear.
- Stress; underlies RAS in some cases and ulcers appear to exacerbate during school or university examination times.
- Trauma; biting the mucosa and trauma from dental appliances may lead to some aphthae.
- Endocrine factors may be relevant in some women. RAS are clearly related to the fall in progestogen level in the luteal phase of the menstrual cycle, and they may then regress temporarily in pregnancy.
- Allergies to food occasionally underlie RAS, and there is a high incidence of atopy.

- Sodium lauryl sulphate (SLS), a detergent in some toothpastes and other oral hygiene products, may produce oral ulceration.
- Immune deficiencies may sometimes be a factor. Ulcers similar to RAS may be seen in HIV and some other immune defects.
- Drugs, especially non-steroidal anti-inflammatory drugs (NSAIDs) and nicorandil, may produce lesions clinically similar to RAS.

Aetiology and pathogenesis

The aetiology of RAS is not entirely clear, and aphthae are therefore termed 'idiopathic'. Indeed, RAS may not be a single condition but rather may be the manifestation of a group of disorders of quite different aetiology (Table 15.1). Despite many studies trying to identify a causal micro-organism, RAS does not at present appear to be infectious, contagious, or sexually transmitted.

Immune mechanisms that appear to play a role in a people with a genetic predisposition to oral ulceration include:

- T-helper cells, which predominate in the early RAS lesions, along with some natural killer (NK) cells.
- Cytotoxic cells then appear in the lesions and there is evidence for an antibody-dependent cellular cytotoxicity (ADCC) reaction. Mononuclear cells, T cells, neutrophils and NK cells may therefore be involved.
- Cross-reacting antigens between the oral mucosa and microorganisms may be involved. Nevertheless, thus far, attempts to implicate a variety of bacteria or viruses in the aetiology have failed. Reactions to heat shock proteins (HSP) are one possibility. Patients with RAS have circulating lymphocytes reactive with peptide 91-105 of HSP 65-60.
- There is no evidence that RAS is a classical autoimmune disease, since there is no association with systemic autoimmune disorders, none of the common autoantibodies are found, and RAS tends to resolve sponta-

Table 15.1 Clinical characteristics of the different presentations of RAS

	Minor	Major	Herpetiform
Percentage of all aphthae	75-85	10-15	5-10
Size (mm)	2-5	>10	<5
Duration (days)	10-14	>14	10-14
Scarring	No	Yes	No

neously with increasing age. Also, in most instances the serum immunoglobulin levels are normal.

- It now seems likely, therefore, that a minor degree of immunological dysregulation underlies aphthae.

Clinical features

Patients with RAS have no clinically detectable systemic symptoms or signs; if ulceration affects the genitals or other mucosae, the diagnosis cannot be of RAS alone.

There are three main clinical types of RAS, though any significance of these distinctions is unclear (they could be three distinct disorders):

- minor aphthous ulcers (80% of all RAS)
- major aphthous ulcers
- herpetiform ulcers.

Minor aphthous ulcers (MiAU; Mikulicz ulcer)

This type of RAS:

- occur mainly in the 10–40 year age group
- often cause minimal symptoms
- are small round or ovoid ulcers 2–4 mm in diameter (Fig. 15.1)
- ulcer floors are initially yellowish but assume a greyish hue as healing and epithelialisation proceeds
- are surrounded by an erythematous halo and some oedema
- are found mainly on the non-keratinised mobile mucosa of the lips, cheeks, floor of the mouth, sulci or ventrum of the tongue



Figure 15.1 Minor aphthae

- occur in groups of only a few ulcers (1–6) at a time
- heal in 7–10 days
- recur at intervals of 1–4 months
- leave little or no evidence of scarring.

Major aphthous ulcers (MjAU)

This type of RAS, also known as Sutton's ulcers or periaadenitis mucosa necrotica recurrens (PMNR):

- are round or ovoid
- reach a large size, usually about 1 cm in diameter or even larger
- are found on any area of the oral mucosa, including the keratinised dorsum of the tongue or palate (Fig. 15.2).
- occur in groups of only a few ulcers (1–6) at one time
- heal slowly over 10–40 days
- recur extremely frequently
- may heal with scarring
- occasionally are found with a raised erythrocyte sedimentation rate or plasma viscosity.

Herpetiform ulceration (HU)

This type of RAS:

- are found in a slightly older age group than the other RAS
- are found mainly in females.
- begin with vesiculation which passes rapidly into multiple minute pinhead-sized discrete ulcers (Fig. 15.3).
- increase in size and coalesce to leave large, round, ragged ulcers
- involve any oral site, including the keratinised mucosa



Figure 15.2 Major aphthae



Figure 15.3 Herpetiform ulcers

- heal in 10 days or longer.
- are often extremely painful
- recur so frequently that ulceration may be virtually continuous.

Diagnosis

Diagnosis of RAS is based on the history and clinical features, as no specific tests are available (Fig. 15.4). Biopsy is rarely indicated, and is only usually needed where a different diagnosis is suspected. However, to exclude the systemic disorders discussed above, it is often useful to undertake:

- a full blood picture
- haemoglobin
- white cell count and differential
- red cell indices
- iron studies (usually assay of serum ferritin levels)

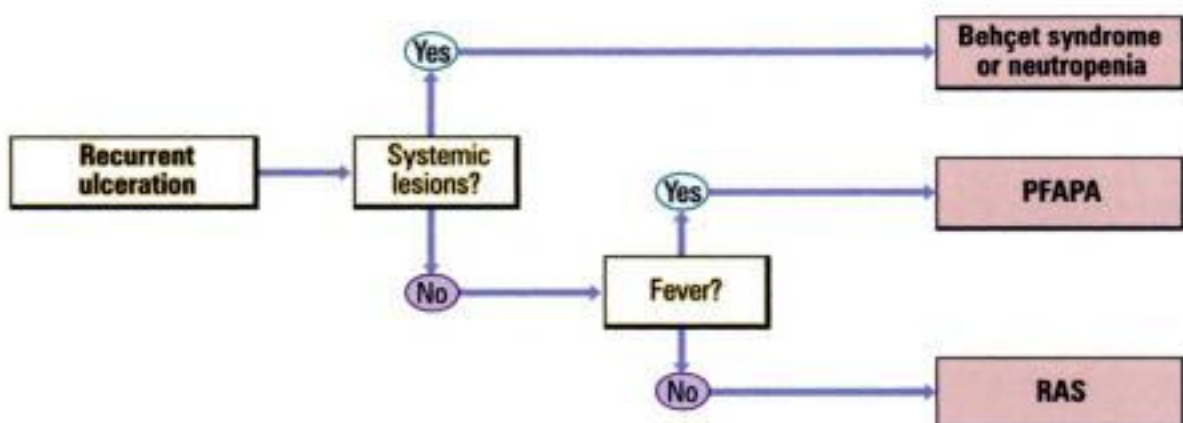


Figure 15.4 Algorithm for recurrent ulceration

- red cell folate assay
- serum vitamin B₁₂ measurements
- serum antiendomysium antibody assay (positive in coeliac disease).

Management

RAS are treated by exclusion of other disorders if suspected. Aphthae or aphthous-like ulcers are also seen in:

- Haematinic deficiencies, mainly deficiencies of iron, folate and B vitamins, especially B₁₂.
- Gastrointestinal disease, especially coeliac disease and Crohn's disease.
- Behçet syndrome, where RAS are seen along with ulcers of the genitals.
- HIV infection, cyclical neutropenia and other immunodeficiencies may present with ulcers that resemble RAS, but tend to be larger and more persistent.
- Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome in children, which includes typical RAS, resolves spontaneously and rarely has long-term sequelae. Corticosteroids are highly effective symptomatically; tonsillectomy and cimetidine treatment have been effective in a few patients.
- Sweet syndrome, in which oral ulcers are found with conjunctivitis, episcleritis and inflamed tender skin papules or nodules.
- Predisposing factors should be corrected (Fig. 15.5):

Patient information sheet

APHTHOUS ULCERS

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- These are common.
- The cause is not known.
- Children may inherit ulcers from parents.
- Aphthous ulcers are not thought to be infectious.
- Some deficiencies or diseases may predispose to ulcers.
- No long-term consequences are known.
- Blood tests and biopsy may be required.
- Ulcers can be controlled but rarely cured.
- Useful website: www.openseason.com/annex/library/cic/X0033_fever.txt.html.

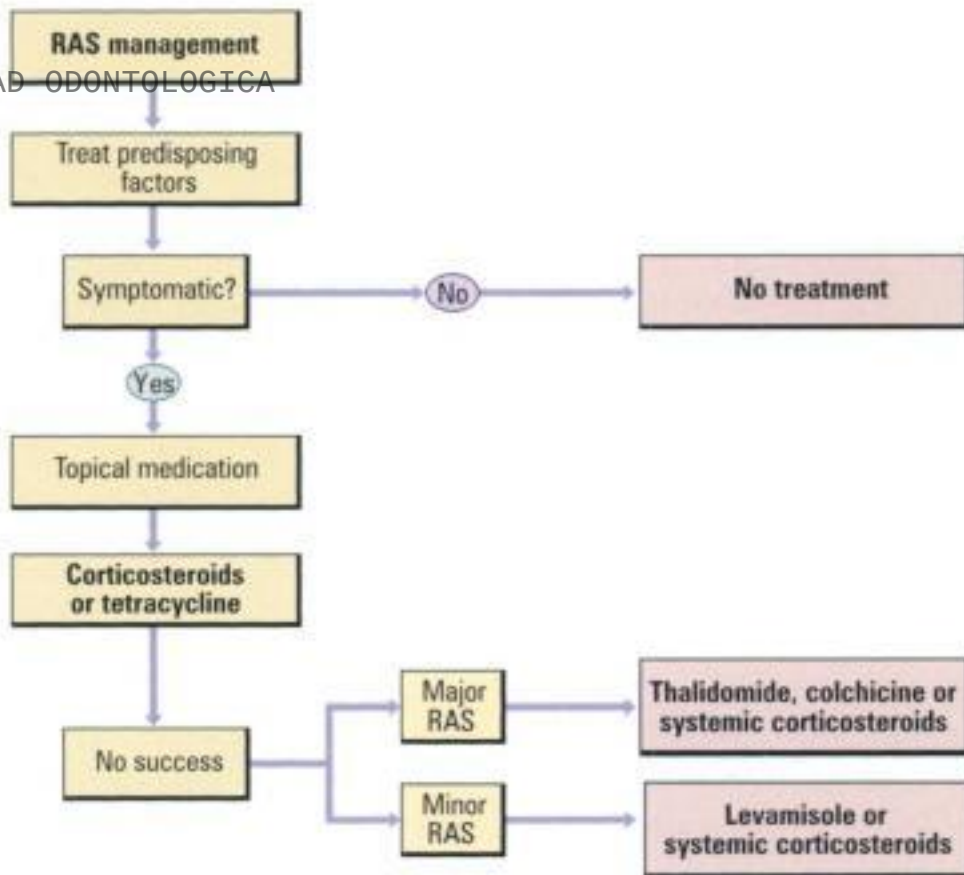


Figure 15.5 Algorithm for RAS management

- ensure that patients brush their teeth atraumatically (e.g. by using a small-headed, soft toothbrush), and avoid particularly hard or sharp foods (e.g. toast, potato crisps) or other trauma to the oral mucosa
- if SLS is implicated, this should be avoided
- any iron or vitamin deficiency should be corrected, once the cause of that deficiency has been established
- if there is an obvious relationship to certain foods, these should be excluded from the diet; patch-testing to reveal allergies may be indicated
- the occasional patient who relates ulcers to the menstrual cycle or to an oral contraceptive may benefit from suppression of ovulation with a progestogen, or a change in the oral contraceptive
- causal drugs should be excluded.
- Relief of pain and reduction of ulcer duration.

Fortunately, the natural history of RAS is one of eventual remission in most cases. However, this may take several years and thus treatment is indicated if the patient has significant discomfort.

- Topical corticosteroids can often control RAS. The major concern of adrenal suppression with long-term and/or repeated application has

rarely been addressed, although the preparations noted below appear not to cause this problem:

- topical hydrocortisone hemisuccinate pellets (Corlan), 2.5 mg
- topical triamcinolone acetonide in carboxymethyl cellulose paste (Adcortyl in Orabase), four times daily
- stronger topical corticosteroids (e.g. betamethasone sodium phosphate as a 0.5 mg tablet dissolved in 15 ml water to make a mouth rinse used four times daily).
- Topical tetracycline (a capsule of 250 mg in 10 ml water) as a mouth rinse, or tetracycline 500 mg plus nicotinamide 500 mg four times daily may provide relief and reduce ulcer duration, but should be avoided in children under 12 years old who might ingest the tetracycline and develop tooth staining.
- Good oral hygiene should be maintained; chlorhexidine or triclosan mouthwashes may help.
- Anti-inflammatory agents; there is a spectrum of topical agents such as benzydamine and amlexanox that may help in the management of RAS.
- If RAS fails to respond to these measures, systemic immunomodulators may be required, under specialist supervision. These include:
 - levamisole
 - colchicine
 - corticosteroids systemically (e.g. prednisolone)
 - thalidomide.

Websites

<http://www.entnet.org/cankerfever.html>

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Atypical Facial Pain

Introduction

Atypical facial pain (AFP) is a constant chronic orofacial discomfort or pain, which is defined by the International Headache Society as "facial pain not fulfilling other criteria". Therefore, it is a diagnosis reached only by the exclusion of organic disease. It falls into the category of medically unexplained symptoms (MUS), most of which appear to have a psychogenic basis. It must be recognized, however, that a patient in pain may well also manifest psychological reactions to the experience.

Atypical facial pain is a constant chronic orofacial discomfort or pain and is often of a dull boring or burning type of pain of ill-defined location.

Other characteristics are:

- a total lack of objective signs
- a negative result from all investigations
- no clear explanation as to cause
- poor response to treatment.

Incidence

Atypical facial pain is fairly common, probably around 1–2% of the population suffer from it.

Age

Patients are often middle-aged or older.

Sex

Patients are often women ($\geq 70\%$).

Geographic

There are no geographic factors implicated.

Predisposing factors

There are often recent adverse life events, such as bereavement or family illness and/or dental or oral interventional procedures.

Aetiology and pathogenesis

The mouth and para-oral tissues have among the richest sensory innervation in the body. Furthermore, a large part of the sensory homunculus on the cerebral cortex receives information from orofacial structures. Right from infancy the mouth is concerned intimately with the psychological development of the individual, and disorders of structures such as the lips, teeth and oral mucosa can hold enormous emotional significance. It is hardly surprising, therefore, that orofacial disorders can result in considerable stress and that there are a range of psychogenic types of orofacial pain, including atypical facial pain.

Positron emission tomography in persons with AFP shows enhanced cerebral activity, suggesting an enhanced alerting mechanism in response to peripheral stimuli. This may lead to the release of neuropeptides and the production of free radicals, causing cell damage, and the release of pain-inducing eicosanoids such as prostaglandins. Most sufferers from AFP are otherwise normal individuals who are or have been under extreme stress, such as bereavement or concern about cancer. However, some have personality traits such as hypochondriasis or neuroses (often depression), and a very few have psychoses.

Clinical features

History

- The pain is mainly in the upper jaw.
- The location of the pain is unrelated to the anatomical distribution of trigeminal nerve innervation.

- The pain is poorly localised, and sometimes crosses the midline to involve the other side, or moves to another site.
- The pain persists for much or all of the day, but does not waken the patient from sleep.
- Pain is often of a deep, dull boring or burning type and chronic.
- There are often multiple oral and/or other psychogenic related complaints, such as:
 - dry mouth
 - bad taste
 - headaches
 - chronic back pain
 - irritable bowel syndrome
 - dysmenorrhoea.
- There is a high level of utilization of healthcare services. There have often already been multiple consultations and attempts at treatment.
- Patients only uncommonly use analgesics to try and control the pain.
- Pain is accompanied by altered behaviour, anxiety or depression. Over 50% of such patients are depressed or hypochondriacal, and some have lost or been separated from parents in childhood. Many lack insight and will persist in blaming organic diseases (or the clinician!) for their pain.

Examination and investigations

The findings on examination include:

- no erythema, tenderness or swelling in the area
- no obvious odontogenic or other local cause for the pain
- total lack of objective physical (including neurological) signs.

Investigation findings include:

- all imaging studies are negative
- all blood investigations are negative.

Diagnosis

This is a clinical diagnosis, though careful examination of the mouth, peri-oral structures and cranial nerves, and imaging (tooth/jaw/sinus radiography and MRI/CT scan) to exclude organic disease such as space-occupying or demyelinating diseases, are important. Most orofacial pain is of local cause – especially dental.

Management

Few patients have spontaneous remission and thus treatment is indicated (Fig. 16.1).

- Cognitive-behavioural therapy or a specialist referral may be indicated. Patient information is a very important aspect in management.
- A technique termed 'retribution' helps these patients; it involves demonstrating an understanding of the complaints by taking a history of related physical, mood and social factors, making the patient feel understood and supported, and making the link between the symptoms and psychological problems. The physician should:
 - Clearly acknowledge the reality of the patient's symptoms and distress and never to attempt to trivialise or dismiss them.
 - Try and explain the psychosomatic background to the problem, ascribing the symptoms to causes for which the patient cannot be blamed.
 - Set goals, which include helping the patient cope with the symptoms rather than attempting any impossible cure.
 - Avoid repeat examinations or investigations at subsequent appointments, since this only serves to reinforce illness behaviour and health fears.

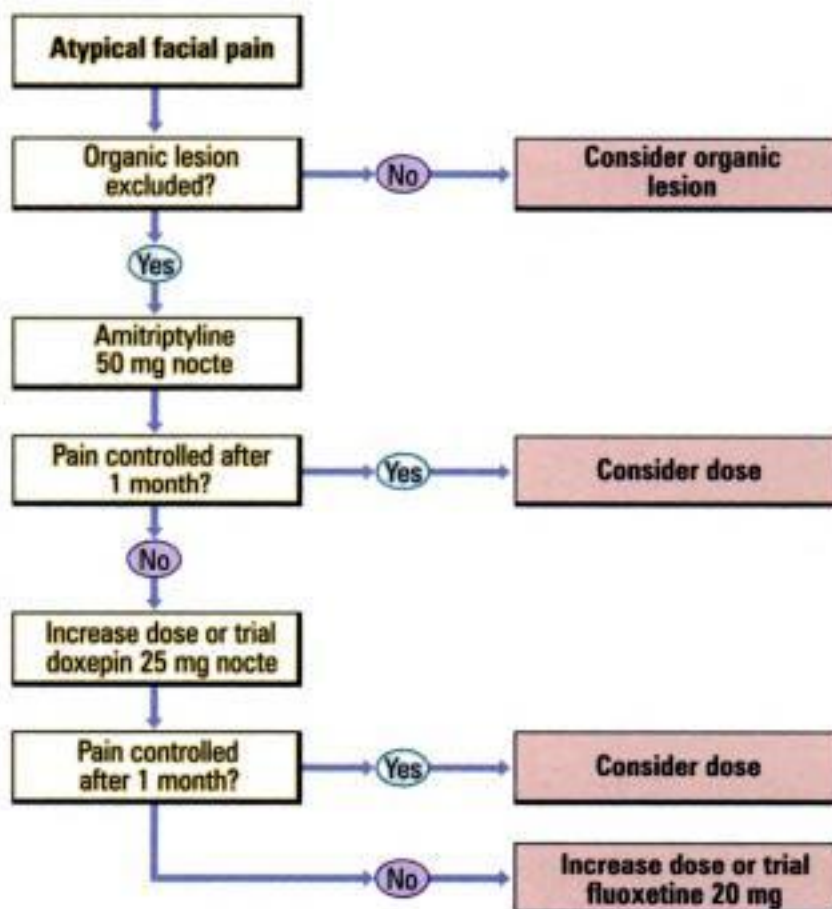


Figure 16.1 Algorithm for atypical facial pain

- Avoid attempts at relieving pain by operative intervention such as restorative treatment, endodontia or exodontia, since these are rarely successful; indeed, any active dental or oral surgical treatment, in the absence of any specific indication, should be avoided.
- Offer referral to a specialist, or a trial of antidepressants, explaining that they are being used to treat the symptoms rather than any depression and that antidepressants have been shown in controlled trials to be effective for this problem, even in non-depressed persons. The pain reduction achieved with antidepressants exceeds that produced by placebos. Also, although antidepressants must be given for at least 2–3 weeks to achieve any antidepressive effect, many patients with MUS such as AFP show benefit within 1 week.
- Medication used includes one of the following regimens:
 - amitriptyline
 - doxepine
 - trazodone
 - prothiadine
 - fluoxetine.

Atypical odontalgia

Atypical odontalgia is pain and hypersensitive teeth in the absence of detectable pathology. The pain is typically indistinguishable from pulpitis or periodontitis but is aggravated by dental intervention. It is probably a variant of atypical facial pain, and should be managed similarly.

Patient information sheet

ATYPICAL FACIAL PAIN

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- This is fairly common.
- The cause is not completely known.
- It is not inherited.
- It may be caused by increased nerve sensitivity.
- There may be a background of stress.
- There are usually no serious long-term consequences.
- X-rays and blood tests may be required.
- Treatment takes time and patience; some nerve-calming drugs can help.
- Useful website: <http://www.facial-neuralgia.org/conditions/atfp.html>.

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Behçet Syndrome

Introduction

Behçet syndrome (BS), also known as Adamantiades syndrome and Behçet's disease, is the association of the triple symptom complex of recurrent aphthous stomatitis (RAS) with genital ulceration and eye disease (especially iridocyclitis), though a number of other systemic manifestations may also be seen.

Incidence

BS is rare, with an occurrence of one case per 100,000 in the developed world, but the frequency is ten-fold higher in the Middle East.

Age

Onset of the disease is usually between the ages of 20 and 30 years.

Sex

BS affects twice as many men as women.

Geographic

The disease is found worldwide, but it is most common in the eastern Mediterranean countries and along the silk route taken by Marco Polo in eastern Asia, China, Korea and Japan. In those countries, BS is a leading cause of blindness, though this is not the case in the western world.

Predisposing factors

There is a genetic predisposition with an association with HLA-B5 and especially HLA-B51 (B5101). HLA-B51 or its B101 allele is significantly associated with BD in Japan, Korea, Turkey and France, as well as with the ocular manifestations in Britain. MICA allele is a polymorphic MHC class I related gene A (MICA) family. MICA6 allele, thought to be in linkage disequilibrium with HLA-B51, and recently shown to be significantly associated with BS in Japan and France. There are no proven predisposing factors, though at various times foods such as pork and walnuts have been suggested.

Aetiology and pathogenesis

Behçet syndrome has not been proved to be infectious, contagious, or sexually transmitted.

- There are many immunological findings in Behçet syndrome similar to those seen in RAS, with various T lymphocyte abnormalities (especially T suppressor cell dysfunction) and increased polymorphonuclear leukocyte motility.
- The antigen responsible has not been identified. A viral aetiology (possibly herpes simplex virus) has been proposed and *Streptococcus sanguis* has been implicated.
- The multiplicity of aetiological factors may have a common denominator in the heat shock proteins (HSP), particularly 65 kDa microbial HSP, which shows significant homology with the human 60 kDa mitochondrial HSP. Indeed, the uncommon serotypes of *Streptococcus sanguis* found in Behçet syndrome cross-react with the 65 kDa HSP, which also shares antigenicity with an oral mucosal antigen. T-cell epitope mapping has identified four peptides derived from the sequence of the 65 kDa HSP that stimulate specifically TCR⁺ lymphocytes from patients with Behçet syndrome.
- There is also a decreased T helper (CD4)/T suppressor (CD8) ratio, antibody-dependent cellular cytotoxicity to oral epithelial cells and evidence of disturbance of natural killer cell activity and increased proinflammatory cytokines such as interferon, interleukin-12 and interleukin-6.
- Circulating autoantibodies against a number of components, including intermediate filaments found in mucous membranes, cardiolipin and neutrophil cytoplasm, are present.
- Circulating immune complexes and changed levels of complement are found, and there is immunoglobulin and complement deposition within

and around blood vessel walls and raised levels of acute phase proteins; **many of the clinical features of Behçet syndrome (erythema nodosum, arthralgia, uveitis)** are also common to established immune complex diseases/vasculitis.

- Vasculitis, usually leukocytoclastic vasculitis, is the common denominator in Behçet syndrome. Immunocytes, (mostly CD4 cells), B cells, and neutrophils infiltrate perivascularly. Prostanoid synthesis in endothelial cells or vessel walls is impaired, whereas von Willebrand factor, endothelin-1,2, thromboxane and thrombomodulin are increased and, hypercoagulability is a feature

Clinical features

Behçet's syndrome is a chronic multisystem and sometimes life-threatening disorder characterised mainly by:

- Recurrent aphthous stomatitis; in 90–100% of cases (Fig. 17.1). RAS is the most common and usually the initial manifestation of Behçet syndrome. However, only few patients with RAS progress to Behçet syndrome and it is not possible to determine in which patients or when the transition may occur. Recent HLA and immunological findings may eventually help in this respect.
- Recurrent painful genital ulcers that tend to heal with scars: in 64–88% of cases. Genital ulcers are especially common in females with BS, and resemble RAS.
- Ocular lesions; uveitis with conjunctivitis (early) and hypopyon (late), retinal vasculitis (posterior uveitis), iridocyclitis and optic atrophy can be present. The most common ocular manifestation is relapsing iridocyclitis, but uveitis, retinal vascular changes and optic atrophy may occur.



Figure 17.1 Aphthae in Behçet syndrome: the most common feature

- CNS lesions are predominantly subtentorial (cerebellum, brainstem and spinal cord), with meningoencephalitis, cerebral infarction, psychosis, cranial nerve palsies, cerebellar and spinal cord lesions, and hemi- and quadriparesis.
- Skin lesions include erythema nodosum-like lesions, papulopustular lesions and acneiform nodules. Venepuncture is, in some patients, followed by pustulation, but this phenomenon (pathergy), said to be characteristic of Behçet syndrome, is not seen often in UK or US patients.
- The joints, epididymis, heart, intestinal tract, vascular system and most other systems may also be involved. Large vein thrombosis (of the inferior vena cava and cranial venous sinuses) can be life-threatening.

However, several non-specific signs and symptoms, which may be recurrent, may precede the onset of the mucosal membrane ulcerations by 6 months to 5 years. These include:

- malaise
- anorexia
- weight loss
- generalised weakness
- headache
- perspiration
- decreased or elevated temperature
- lymphadenopathy
- pain of the substernal and temporal regions.

A history of repeated sore throats, tonsillitis, myalgias, and migratory arthralgias without overt arthritis is common.

Diagnosis

Because Behçet syndrome is rare and the symptoms overlap those of many other diseases, it can be very difficult to diagnose.

The International Study Group for Behçet's Disease criteria suggest the diagnosis be made on clinical grounds alone on the basis of RAS plus two or more of:

- recurrent genital ulceration
- eye lesions
- skin lesions
- pathergy - a >2 mm diameter erythematous nodule or pustule forming 24-48 hours after sterile subcutaneous puncture of the forearm skin.

Major criteria for diagnosis of Behçet syndrome include:

● **RAS** PDFFREE COMMUNAD ODONTOLOGICA

- genital ulcers
- ocular lesions
- CNS lesions
- skin lesions.

Minor criteria for diagnosis are:

- Arthralgia: large joint arthropathies that are subacute, non-migratory, self-limiting and non-deforming.
- Superficial or deep migratory thrombophlebitis, especially of the lower limbs. Thromboses of large veins, such as the dural sinuses or venae cavae, can be life-threatening.
- Intestinal lesions: inflammatory bowel disease with discrete ulcerations.
- Lung disease: pneumonitis.
- Renal disease: haematuria and proteinuria.

The major limitation of these diagnostic criteria, however, lies in the fact that recurrent oral ulceration is the key for diagnosis of Behçet syndrome. For example, patients with uveitis and genital ulcers, without oral aphthosis, would not be considered to have Behçet syndrome, although this may in fact be a far-advanced form of Behçet syndrome.

Investigations

Findings of HLA-B5101, raised serum IgD and antibodies to cardiolipin are supportive. Antineutrophil cytoplasmic antibodies, antiphospholipid antibodies, rheumatoid factors and antinuclear antibodies are usually negative.

Disease activity may be assessed by serum levels of acute-phase proteins or antibodies to intermediate filaments, both of which are raised in active Behçet syndrome. Erythrocyte sedimentation rate, C-reactive protein and other acute-phase reactants may be elevated during the active stage. Increase of α_2 -globulins is often seen. Serum immunoglobulins, especially IgA, may be elevated. Circulating immune complexes are often present.

Differential diagnosis

This is from other oculomucocutaneous syndromes:

- Sweet syndrome: oral ulcers, conjunctivitis, episcleritis, inflamed tender skin papules or nodules.
- Erythema multiforme: erosions, target (iris) lesions.
- Pemphigoid: bullae, erosions.
- Pemphigus: erosions, flaccid skin bullae.

- Reiter syndrome: ulcers, conjunctivitis, keratoderma blenorrhagica.
- Ulcerative colitis.
- Herpes simplex virus.
- Syphilis.
- Lupus erythematosus.
- Mixed connective tissue disease.

Management

Chronic morbidity is usual in Behçet syndrome; the main problem is ophthalmic involvement, which can result in blindness. The effects of the disease may be cumulative, especially with neurological, vascular and ocular involvement. Mortality is low, but can occur from neurological involvement, vascular disease, bowel perforation or cardiopulmonary disease, or as a complication of immunosuppressive therapy. In the face of such serious potential complications, patients with suspected Behçet syndrome should be referred early for specialist advice. Patient information is also an important aspect in management.

- Topical treatment for RAS includes tetracycline mouthwash and topical corticosteroids.
- Systemic treatment includes mainly colchicine.
- Other systemic treatments include corticosteroids, azathioprine, ciclosporin, chlorambucil, cyclophosphamide, dapsone, interferon- α , levamisole or thalidomide.

Websites

American Behçet's Association: <http://www.w2.com/behcets.html>

<http://www.aarda.org/indexf.html>

<http://www.emedicine.com/derm/topic49.htm>

Further reading

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18

PDFFREE COMUNIDAD ODONTOLOGICA

Bell's palsy

Introduction

The facial nerve not only carries nerve impulses to the muscles of the face, and facial expression, and to the stapedius muscle of the stirrup bone (the stapes) in the middle ear, but also carries secretomotor fibres to the tear (lacrimal) glands, and to the saliva glands. It also transmits taste from the anterior tongue. Since the function of the facial nerve is so complex, many symptoms may occur if it is disrupted. Bell's palsy is an acute lower motor neurone paralysis (palsy) of the face:

- no local or systemic cause can be identified (it is idiopathic)
- there is inflammation of the facial nerve with demyelination, usually in the stylomastoid canal, and oedema further hazarding the blood supply to the nerve
- it may be immunologically mediated and associated with infection, commonly by herpes simplex virus (HSV).

Incidence

Bell's palsy is rare, at possibly around 10 cases per 100,000 population. However, it represents about 50% of all facial palsies.

Age

Usually found in the young adult.

Sex

Both sexes can be affected.

Geographic

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No geographic factors are known.

Predisposing factors

Predisposing factors, found in a minority of cases, include:

- pregnancy
- hypertension
- diabetes
- lymphoma.

Aetiology and pathogenesis

Bell's palsy is most commonly caused by inflammation and oedema in the facial nerve canal, usually in the stylomastoid canal, causing demyelination of the facial nerve (seventh cranial nerve) (Table 18.1).

This is usually associated with herpes simplex virus (HSV) or, rarely, another infectious microorganism such as:

- Another herpesvirus:
 - varicella-zoster virus (VZV) infection
 - Epstein-Barr virus (EBV) infection
 - cytomegalovirus (CMV) infection
 - human herpesvirus-6 infection.
- A retrovirus:
 - HIV infection
 - HTLV-1 infection.
- A bacterium:
 - otitis media
 - Lyme disease.
- Kawasaki disease (if this has a microbial cause; see Ch. 37).

Clinical features

Damage to the facial nerve may result in twitching, weakness, or paralysis of the face, in dryness of the eye or the mouth, and/or in disturbance of taste or hearing. There is:

- Acute onset of paralysis over a few hours, maximal within 48 hours.
- Paralysis of the upper and lower face.

Table 18.1 Localisation of site of lesion in, and causes of, unilateral facial palsy

Muscles paralysed	Lacrimation	Hyperacusis	Sense of taste	Other features	Probable site of lesion	Type of lesion
Lower face	N	-	N	Emotional movement retained $\pm$ monoparesis or hemiparesis $\pm$ aphasia	Upper motor neurone	Stroke, brain tumour, trauma, HIV infection
All facial muscles	$\downarrow$	+	$\downarrow$	$\pm$ Vth nerve damage	Lower motor neurone Facial nucleus	Multiple sclerosis
All facial muscles	$\downarrow$	+	$\downarrow$	$\pm$ VIIIth nerve damage	Between nucleus and geniculate ganglion	Fractured base of skull, posterior cranial fossa tumours, sarcoidosis
All facial muscles	N	$\pm$	N or $\downarrow$	-	Between geniculate ganglion and stylomastoid canal	Otitis media, cholesteatoma, mastoiditis
All facial muscles	N	-	N	-	In stylomastoid canal or extracranially	Bell's palsy, trauma, local analgesia (e.g. misplaced inferior dental block), parotid malignant neoplasm, Guillain-Barré syndrome
Isolated facial muscles	N	-	N	-	Branch of facial nerve extracranially	Trauma, local analgesia

N, normal; +, present; $\downarrow$, reduced

- Usually only unilateral facial paralysis (Fig. 18.1).
- Diminished blinking and absence of tearing. Together these can reduce or eliminate the flow of tears across the eyeball, resulting in drying, erosion, and ulceration of the cornea and the potential loss of the eye.
- Occasionally:
 - pain in the region of the ear or in the jaw may precede the palsy by a day or two
 - there may be complaints of facial numbness, but sensation is actually intact on testing
 - if the lesion is located proximal to the stylomastoid canal, there may also be hyperacusis (reduced damping activity of the stapedius because of loss of function of the nerve to the stapedius) or loss of taste (loss of function of the chorda tympani), or loss of lacrimation.
- Up to 10% of patients have a positive family history.
- Up to 10% of patients suffer recurrent episodes.

Diagnosis

The history should be directed to exclude facial palsy caused by other factors, such as:

- Stroke.
- Trauma physically affecting the facial nerve (e.g. in the parotid region or to the base of the skull), or by underwater diving (barotrauma).
- Tumours affecting the facial nerve (e.g. acoustic neuroma or cholesteatoma).
- Inflammatory disorders affecting the facial nerve:
 - multiple sclerosis
 - connective tissue disease
 - sarcoidosis



Figure 18.1 Bell's palsy

- Melkersson-Rosenthal syndrome.

● **Infections affecting the facial nerve:**

- viral infections (HSV, VZV, EBV, CMV, HIV infection, HTLV-1 infection (Japanese and Afro-Caribbean patients mainly)
- bacterial infections (middle ear infections (e.g. otitis media), Lyme disease (camping or walking in areas that may contain deer ticks)).

Idiopathic Bell's palsy is less likely to be the diagnosis if:

- trauma has occurred
- multiple cranial nerves are involved
- there are features consistent with multiple sclerosis
- there are signs of neoplasia
- viral vesicles are present in the palate or ear
- the paralysis is slowly progressive or chronic.

The examination should include:

- A full neurological examination, especially to exclude a stroke, and to exclude lesions involving other cranial nerves (especially the abducens and vestibulocochlear nerves).
- Examination of the facial nerve; weakness is demonstrated by testing the corneal reflex and asking the patient to close the eyes against resistance, raise the eyebrows, raise the lips to show the teeth, and try to whistle.
- Ear and mouth examination to exclude Ramsay-Hunt syndrome; herpes zoster of the facial nerve ganglion (geniculate ganglion), which causes lesions in the palate and ipsilateral ear, and facial palsy.
- Ear examination, for discharge and other signs of middle ear disease.

Investigations which may be indicated include:

- A test for the degree of nerve damage; facial nerve stimulation or needle electromyography may be useful, as may electrogustometry, nerve excitability tests, electromyography and electroneuronography.
- A test for loss of hearing; pure tone audiometry is often used.
- A test for taste loss.
- A test for balance.
- A test for tear production. Schirmer's test, in which a strip of filter paper is placed in the lower conjunctival fornix, and the amount of tear production measured, is usually used.
- Magnetic resonance imaging or computed tomography imaging of the internal auditory meatus, cerebellopontine angle and mastoid may be needed to exclude an organic lesion such as a tumour – particularly in progressive facial palsy.
- Blood pressure measurement to exclude hypertension.
- Blood tests, which may include:

• fasting blood sugar levels (to exclude diabetes)

• tests for HSV or other virus infections such as HIV may need to be considered

• serum angiotensin converting enzyme levels to exclude sarcoidosis

• serum antinuclear antibodies to exclude connective tissue disease

• in some areas, Lyme disease (tick-borne infection with *Borrelia burgdorferi*) should be excluded by enzyme-linked immunosorbent assay (ELISA).

● Occasionally, a lumbar puncture is required.

Management

Most patients with Bell's palsy (up to 85%) improve spontaneously within a few weeks. However, the after-effects in the remaining 15–40% can be so severe and distressing, that active treatment is warranted. The prognosis can be assessed on several factors:

● Favourable prognostic signs include:

• incomplete paralysis in the first week

• persistence of the stapedial reflex, measured by electroneurography.

● Bad prognostic signs include:

• an initially complete paralysis (then only 50% recover completely within a week, and few who have not recovered by 2 weeks will do so)

• hyperacusis

• severe taste impairment

• diminished lacrimation or salivation, especially if in older, diabetic or hypertensive patients.

Treatment with systemic corticosteroids results in 80–90% complete recovery. There is thus a strong argument for treating all patients with prednisolone. Since HSV is frequently implicated, antivirals (usually aciclovir) are also justifiably used. Patient information is also an important aspect in management. Complications include:

● The commonest complication of Bell's palsy is corneal dryness and scarring due to inadequate eyelid closure. Therefore, during the acute phase, the cornea should be protected with an eye pad. Synthetic tears (hypromellose drops) may help. Protective glasses or clear eye patches are often used to keep the eye moist and to keep foreign materials from entering the eye.

● If paralysis persists and function remains incomplete, the palpebral fissure may narrow, the nasolabial fold deepens and there may be leakage of saliva from the commissure.

Burning Mouth Syndrome (Oral Dysaesthesia)

Introduction

Burning mouth 'syndrome' (BMS) – also known as glossopyrosis, glossodynia, oral dysaesthesia or stomatodynia – is the term used when symptoms described usually as a burning sensation, exist in the absence of identifiable organic aetiological factors: it is a medically unexplained symptom (MUS).

Incidence

BMS is a fairly common chronic complaint, affecting up to 5 persons per 100,000 population.

Age

BMS is seen especially in middle-aged or elderly patients.

Sex

BMS is seen especially in females, in a ratio of about 3:1.

Geographic

BMS is seen worldwide.

Predisposing factors, aetiology and pathogenesis

- No precipitating cause for BMS can be identified in over 50% of the patients.
- A psychogenic cause, such as anxiety, depression or cancerophobia, can be identified in about 20% of cases.
- In the others, BMS appears to follow either:
 - dental intervention
 - an upper respiratory tract infection
 - use of drugs such as ACE or protease inhibitors (Fig. 19.1).
- There is no specific relationship to hormonal changes, despite the fact that BMS is often seen in middle-aged or elderly peri- or post-menopausal females.
- Defined clinical conditions that must be excluded, since they can also present with burning, include (Table 19.1):
 - erythema migrans (geographic tongue)
 - lichen planus
 - dry mouth
 - candidiasis
 - glossitis such as may be associated with haematinic (iron, folic acid, vitamin B) deficiency
 - diabetes.
- Organic problems with no detectable clinical lesions that can cause symptoms similar to BMS include:
 - a haematological deficiency state (deficiencies in iron, folic acid or vitamin B) in about 30%
 - restricted tongue space from poor denture construction
 - parafunction, such as nocturnal bruxism or tongue-thrusting
 - neuropathy, such as follows damage to the chorda tympani nerve
 - thyroid hypofunction
 - drugs such as ACE inhibitors and protease inhibitors.

Clinical features

BMS most frequently affects the tongue, but it can also affect the palate or, less commonly, the lips or lower alveolus. Three types of BMS have been described on the basis of the pattern of symptoms of burning sensation (Table 19.2).

The history is that the burning sensation is:

- Chronic.
- Usually bilateral.

- Often relieved by eating and drinking, in contrast to pain caused by organic lesions which is typically aggravated by eating. Alcohol may reduce the symptoms.

There are often multiple oral and/or other psychogenic-related complaints, such as:

- dry mouth
- bad or altered taste
- thirst
- headaches
- chronic back pain

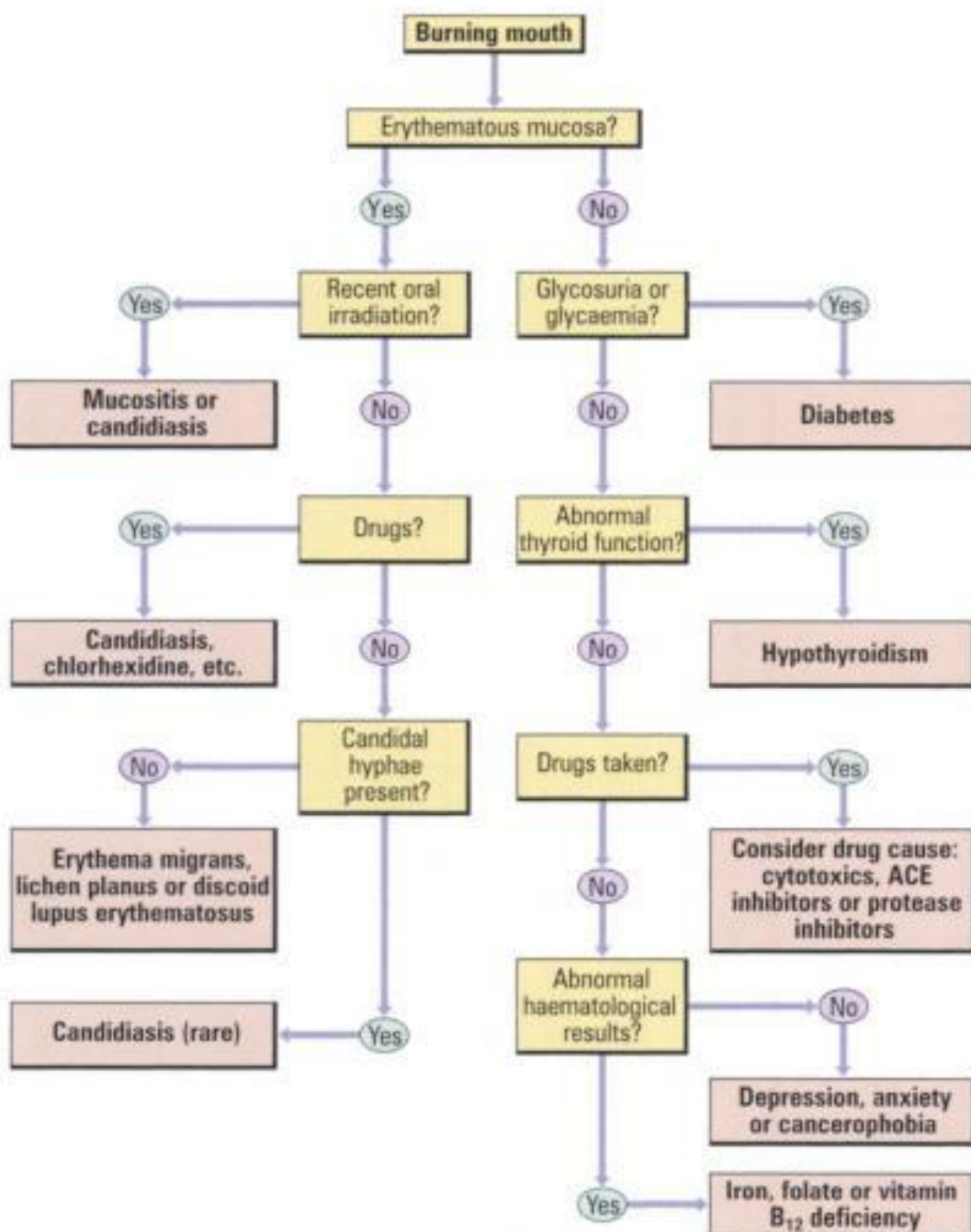


Figure 19.1 Algorithm for burning mouth syndrome

Table 19.1 Causes of a burning sensation in the mouth**Local causes**

- Erythema migrans (geographical tongue)
- Lichen planus
- Candidiasis
- Denture problems

Systemic causes

- Psychogenic
- Cancerophobia
- Depression
- Anxiety states
- Hypochondriasis
- Deficiency of:
 - vitamin B, especially B₁₂
 - folate
 - iron
- Dry mouth
- Diabetes
- Drugs such as ACE inhibitors

Table 19.2 Types of burning mouth syndrome

Type	Symptom pattern	Frequency	Other features
1	No symptoms on waking, but increasing during the day	Unremitting	–
2	Symptoms on waking and through the day	Most common	Unremitting
3	No regular pattern of symptoms	Least common	May remit

- irritable bowel syndrome
- dysmenorrhoea.

There may be changes in sleep patterns and mood and there have often already been multiple consultations and attempts at treatment. Patients only uncommonly use analgesics to try to control the symptoms.

Investigations are all negative, and examination shows no:

- clinically detectable signs of mucosal disease
- tenderness or swelling of the tongue or affected area
- neurological or other objective signs.

Diagnosis

Oral examination is important to exclude organic causes of discomfort, such as (see Fig. 19.1):

- erythema migrans (geographic tongue)

- candidiasis

- lichen planus

- dry mouth

- glossitis

- diabetes

- denture problems.

Investigations indicated may include psychological screening using, for example, the Hospital Anxiety and Depression (HAD) scale, and laboratory screening in order to exclude:

- anaemia, a vitamin or iron deficiency (blood tests)

- diabetes (blood and urine analyses)

- thyroid dysfunction (blood analyses)

- xerostomia (salivary flow rates)

- candidiasis (oral rinse).

Management

About 50% of patients with BMS remit spontaneously within 6 or 7 years, but few have spontaneous remission in the short term, and thus treatment is usually indicated.

- Patients should avoid anything that aggravates symptoms, such as sparkling wines, citrus drinks and spices. Patient information is an important aspect in management.

- Reassurance and attention to any factors, such as the dentures or haematinic deficiencies, may be indicated

- Active dental or oral surgical treatment, or attempts at 'hormone replacement', in the absence of any specific indication, should be avoided.

- Cognitive-behavioural therapy or a specialist referral may be indicated. A technique termed 'retribution' helps manage these patients; it involves demonstrating an understanding of the complaints by taking a history of related physical, mood and social factors, making the patient feel understood and supported, and making the link between symptoms and psychological problems.

- It is important to clearly acknowledge the reality of the patient's symptoms and distress and never to trivialise or dismiss them.

- Try and explain the psychosomatic background to the problem, ascribing the symptoms to causes for which the patient cannot be blamed.

Patient information sheet**BURNING MOUTH SYNDROME**

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- This is a common condition.
- The cause is not usually known, but it may be a nerve hypersensitivity.
- It is not inherited.
- It is not infectious.
- It may occasionally be caused by some mouth conditions, dry mouth, deficiencies, diabetes or drugs.
- It has no long-term consequences.
- Blood tests or biopsy may be required.
- Burning mouth syndrome may be controlled by some nerve-calming drugs.

- Set goals which include helping the patient cope with the symptoms rather than attempting any impossible cure.
- Do not repeat examinations or investigations at subsequent appointments, since this only serves to reinforce illness behaviour and health fears.
- Explain that antidepressants, if prescribed, are being used to treat the symptoms not depression, and that antidepressants have been shown in controlled trials to be effective for this problem, whether or not the patient is depressed. The pain reduction achieved with antidepressants exceeds that produced by placebos, but antidepressants must be given for at least 2–3 weeks to achieve any antidepressive effect. However, most patients with MUS show benefit within 1 week. Medication used includes: amitriptyline, doxepine, trazodone, prothiadine, fluoxetine or clonazepam. Some patients respond to other medication: topical benzydamine rinse or spray; topical capsaicin cream 0.025% (Zacin) or 0.075% (Axsain); a clonazepam tablet sucked locally; or α -lipoic acid systemically.

Websites

Burning Mouth Syndrome National Organization for Rare Disorders, Inc. Topic:
<http://www.readersdigesthealth.com/kbase/nord/nord234.htm>

Further reading

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20

PDFFREE COMUNIDAD ODONTOLOGICA

Cancer

Introduction

More than 90% of oral cancer is oral squamous cell carcinoma (OSCC) (Table 20.1). OSCC accounts for a large proportion of cancers in the head and neck. Cancers of the oral cavity are classified according to site by the International Classification of Diseases (ICD):

- lip (ICD 140)
- tongue (ICD 141) (Fig. 20.1)
- gum (ICD 143)
- floor of the mouth (ICD 144)
- unspecified parts of the mouth (ICD 145).

Table 20.1 Oral malignant neoplasms

Common

- Squamous cell carcinoma

Less common

- Salivary gland tumours
- Malignant melanoma
- Lymphomas
- Neoplasms of bone and connective tissue
- Some odontogenic tumours
- Maxillary antral carcinoma (or other neoplasms)
- Metastatic neoplasms (breast, lung, kidney, stomach, liver)
- Langerhans cell histiocytoses
- Kaposi sarcoma

Other malignant oral neoplasms include:

● **Other epithelial malignancies:**

- arising from a surface (e.g. melanoma)
- glandular (e.g. salivary gland)
- intrabony epithelial (e.g. arising in a cyst).

● **Secondary carcinomas:**

- within a lymph node (e.g. metastasis from the mouth)
- within bone (e.g. metastasis from lung or breast cancer).

● **Sarcomas:**

- in muscle (e.g. rhabdomyosarcoma)
- in bone (e.g. osteosarcoma)
- from blood vessels (e.g. Kaposi sarcoma).

● **Lymphoreticular neoplasms.**

Oral squamous cell carcinoma

Incidence

OSCC is among the ten most common cancers worldwide. The number of new mouth (oral) and oropharyngeal cancers are estimated to be 300,000 cases worldwide, amounting to around 3% of total cancers.

Age

OSCC is seen predominantly in the elderly, but intraoral cancer is increasing, especially in younger adults.

Sex

OSCC is seen predominantly in males, but the male/female differential is decreasing.



Figure 20.1 Cancer of the tongue (squamous cell carcinoma)

Geographic

- There is marked inter-country variation in both the incidence of and mortality from oral cancer.
- In addition, there is also growing evidence of intra-country ethnic differences in incidence and mortality, especially recorded in the UK and USA.
- In the developed world:
 - OSCC is uncommon.
 - The incidence of oral cancer varies between countries and between different regions of the same country. For example, parts of France and Newfoundland have the highest incidence in the West, with about ten times the incidence of oral carcinoma in the UK. Also, oral cancer is more than twice as common in Scotland than in England and Wales and, even within Scotland there are regional differences.

Table 20.2 Potentially malignant oral lesions

Lesion	Aetiological factors	Features
Erythroplasia	Tobacco/alcohol	Flat red plaque
Leukoplakia	Tobacco/alcohol, human papilloma virus	White or speckled plaque
Proliferative verrucous leukoplakia	Tobacco/alcohol	White or speckled nodular plaque
Sublingual keratosis	Tobacco/alcohol	White plaque
Actinic cheilitis	Sunlight	White plaque/erosions
Lichen planus	Idiopathic	White plaque/erosions
Submucous fibrosis	Areca nut	Immobile mucosa
Discoid lupus erythematosus	Idiopathic	White plaque/erosions
Chronic candidiasis	<i>Candida albicans</i>	White or speckled plaque
Syphilitic leukoplakia	Syphilis	White plaque
Atypia in immunocompromised patients	? Papilloma virus	White or speckled plaque
Dyskeratosis congenita	Genetic	White plaques
Paterson–Kelly syndrome (sideropenic dysphagia; Plummer–Vinson syndrome)	Iron deficiency	Postcricoid web

- In the developing world, particularly South-East Asia and Brazil: the incidence of oral cancer is the highest in the world but varies widely in different areas
 - there are ethnic differences in incidence, often attributed to lifestyle habits.

Aetiology

Potentially malignant states

Potentially malignant (precancerous) lesions which can progress to OSCC include, especially (Table 20.2):

- Erythroplasia (erythroplakia): the most likely lesion to progress to severe dysplasia or carcinoma.
- Leukoplakia (see Ch. 26):
 - proliferative verrucous leukoplakia
 - sublingual leukoplakia
 - candidal leukoplakia
 - syphilitic leukoplakia.

Potentially malignant (precancerous) conditions include:

- actinic cheilitis
- lichen planus; there are also cases of dysplasia with a lichenoid appearance (lichenoid dysplasia)
- discoid lupus erythematosus
- submucous fibrosis
- atypia in immunocompromised patients
- dyskeratosis congenita
- Paterson–Kelly syndrome (sideropenic dysphagia; Plummer–Vinson syndrome).

One of the main features that appears to precede the onset of malignancy is epithelial dysplasia, a histological term describing the combination of disorderly maturation and disturbed cell proliferation. The changes indicative of dysplasia are shown in Table 20.3. Dysplasia varies in severity, and it is the more severe grades that are associated with higher malignant potential. However, dysplasia does not always indicate a malignant potential, since it can also be seen in regenerating tissue and some non-precancerous lesions such as some:

- ulcers
- viral infections
- candidal infections
- granular cell tumours.

Table 20.3 Microscopic features of epithelial dysplasia**Cell changes**

- Nuclear hyperchromatism
- Increased nucleus/cytoplasm ratio
- Abnormal mitoses
- Mitoses in stratum spinosum
- Pleomorphic cells and nuclei
- Large prominent nucleoli
- Premature and individual cell keratinisation

Tissue changes

- Basal cell hyperplasia
- Bullous or drop-shaped rete pegs
- Loss of epithelial stratification
- Reduced cell cohesion
- Loss of basal cell polarity
- Keratin or epithelial pearls

Predisposing factors (risk factors) for OSCC

- In the developed world, OSCC is seen especially in the following groups:
 - tobacco users
 - alcohol users
 - lower socio-economic groups
 - ethnic minority groups.
- In the developing world, OSCC is seen especially in the following groups:
 - tobacco users
 - alcohol users
 - betel quid users (some 20% of the world's population use betel)
 - lower socio-economic groups.
- A predisposition to OSCC has been attributed mainly to specific risk factors such as tobacco (smoking and smokeless) and alcohol (see below). However, dietary factors as well as the existence of genetic predispositions may also play a part, since neither do all tobacco/alcohol users develop cancer, and equally nor do all patients with cancer have these habits. These other factors may include an impaired ability to metabolise carcinogens and/or to repair DNA damaged by mutagens. Individual susceptibility to cancer may sometimes be explained by a genotype that results in increased carcinogen exposure as a consequence of their carcinogen or procarcinogen metabolism. The list of known carcinogens is long, but many of the most important are aromatic amines (including arylamines and heterocyclic amines). Potential carcinogens may be taken exogenously with full carcinogenic potential (e.g. tobacco and tobacco-contained nitrosamines, or nitrosamines in products such as Toombak) or sometimes they are procarcinogens, i.e. carcinogens may be produced during their metabolism (e.g. acetaldehyde, produced from alcohol by alcohol dehydrogenase, is carcinogenic).

Risk factors: tobacco

Tobacco smoke is a complex mixture of at least 50 compounds including polycyclic aromatic hydrocarbons such as benzpyrene, nitrosamines, aldehydes and aromatic amines. Tobacco habits have varied effects:

- Cigarette smokers appear to be about five times more likely to develop OSCC than are non-smokers. The precise role of cigarette smoking is surprisingly difficult to define, not least because many heavy smokers also drink alcohol and can have other complicating factors. However, studies of those who abstain from such habits (e.g. Mormons, Seventh Day Adventists) have shown a lower incidence of OSCC in those groups.
- Bidi is a type of cigarette made of tobacco rolled in a dried temburni leaf. It is smoked in India and is associated with a high incidence of leukoplakia and oral cancer. Reverse smoking – where the lighted end is held in the mouth, as in parts of India – is linked with a high incidence of OSCC of the hard palate, an otherwise unusual site.
- Cigar smoking may predispose to OSCC, and some studies have shown an association with floor of mouth leukoplakia in women smokers.
- Pipe smoking may be associated with nicotinic stomatitis, a benign non-premalignant condition, but there is evidence from some countries that pipe smoking may be associated with a predisposition to OSCC.
- Tobacco-chewing in peoples from parts of Asia, along with a variety of ingredients in a 'betel quid' (betel vine leaf, betel (areca) nut, catechu, and slaked lime, often together with tobacco) appears to predispose to OSCC, particularly when it is started early in life and is used frequently and for prolonged periods (see below).
- Smokeless tobacco, for example, snuff-dipping in women in south-eastern USA who place snuff in the buccal sulcus, has been shown to predispose to gingival and alveolar carcinoma close to where the snuff is placed.

Risk factors: alcohol

Several studies have shown an association between high alcohol consumption and OSCC. Alcoholic beverages may contain carcinogens or procarcinogens, including:

- ethanol; this is metabolised by alcohol dehydrogenase and to some extent by cytochrome p450 to acetaldehyde, which may be carcinogenic
- nitrosamines
- urethane contaminants.

Many alcoholic drinks also contain congeners and some local brews may contain carcinogens that are probably more responsible for oral cancer than is pure alcohol (ethanol). For example, in parts of France, such as Brittany,

there is a close relationship between the consumption of the alcoholic drink *Calvados*, a not-stilled spirit, and cancer of the oesophagus and mouth.

There were suggestions, based on a small number of patients, and which have now not been confirmed, that the frequent use of proprietary alcohol-containing mouthwashes over prolonged periods predisposes to oral cancer, but only in those patients who neither smoke nor drink alcohol.

Risk factors: betel quid

- Betel quid can be made up at home or purchased as ready to chew. Normally, lime and catechu are smeared on a betel leaf, which is folded and the rest of the ingredients are added. Once folded, the resulting quid is placed in the mouth, usually the cheek, and gently chewed and sucked sometimes for hours.
- Betel quid is widely used, though contents vary in different parts of the world and cultures. Apart from the betel leaf, typical contents are spices, tobacco, areca nut and sometimes slaked lime.
- Betel (paan; the leaf, stem or inflorescence of *Piper betel*) leaves are from the betel vine, a relative of the pepper family.
- Spices; a large variety of additives may be incorporated. In India, catechu, derived from acacia pods and subquality areca, is a red-brown paste which may also be spread on the leaf. It contains a high concentration of tannins and gives astringency to the mixture. In Malaysia, gambir is a similar substance, paler in colour, made from the leaves and shoots of *Uncaria gambir*. Other additives that may be incorporated include cardamom pods, cinnamon, cloves, melon and cucumber seeds. Alternatively, menthol, camphor, sugar balls, rose water, aniseed, mint essences or syrup may be used, as well as a wide range of spices (fennel, turmeric, saffron, cumin, coriander, nutmeg, ginger).
- Tobacco is shredded, sun-dried tobacco from *Nicotina tobaccum* or *Nicotina rustica*. Tobacco may be used directly in the quid, may be raw, sun dried or roasted, and may be strong or mild in flavour. In addition, roasted tobacco leaves can be finely chopped, powdered and scented for use in the quid, or the leaf residue boiled, made into paste and scented with perfume or rose water.
- Areca nut (the seed of *Areca catechu*, sometimes referred to as betel nut, although it is from a different plant than the betel leaf) is the seed of the areca palm, is about the size of a nutmeg and has a thick, fibrous husk.
- Slaked lime (calcium hydroxide) is made from chalk, coral or sea shells, and may be mixed with coconut oil, turmeric water, cream, whey or sugar sweets.
- Other chewing habits, usually containing tobacco, are used in different cultures (e.g. Qat, Shammah, Toombak).

Other risk factors

- Microorganisms such as *Candida* and human papilloma viruses (HPV) have been detected in some potentially malignant lesions and some OSCC where they may play a role. HPV are especially implicated in tonsillar carcinoma. HPV-16 is particularly implicated.
- Actinic radiation may predispose to lip cancer. Facts that support such a relationship include:
 - lip cancer involves the more exposed lower lip, rather than the upper lip
 - there is a higher incidence of lip cancer in outdoor workers and rural populations than in office workers or urban populations
 - fair-skinned people tend more than dark-skinned people to develop lip cancer (as well as skin cancer and melanoma) in sunny climates.
- Immune defects may predispose to OSCC, especially lip cancer. This is increased in, for example, immunosuppressed renal transplant recipients.
- Diets rich in fresh fruits and vegetables and of vitamin A may have a protective effect on oral cancer and pre-cancer.

Summary

In summary, the lifestyle factors implicated in OSCC may include:

- tobacco use
- betel use
- alcoholic beverages
- a diet poor in fresh fruit and vegetables
- in the case of lip carcinoma, exposure to sunlight.

Pathogenesis

OSCC arises as a consequence of multiple molecular events causing genetic damage affecting many chromosomes and genes, which leads to DNA changes.

Genes which are damaged and play crucial roles in carcinogenesis include mainly those involved in cell growth and control:

- Tumour suppressor genes controlling the fate of chromosomally damaged cells and the cell growth cycle, such as p16 and p53.
- Oncogenes involved in cell signalling, such as PRAD-1, Int-2, hst-1, bcl-1 and H-ras.
- Genes for enzymes involved in chromosome shortening (telomerases).
- The accumulation of genetic changes leads to cell dysregulation to the extent that growth becomes autonomous and invasive mechanisms develop – this is carcinoma.

- Non-healing extraction socket.
- Lesion fixed to deeper tissues or to overlying skin or mucosa.
- Lymph node enlargement, especially if there is hardness in a lymph node or fixation. Enlarged cervical nodes in a patient with oral carcinoma may be caused by infection, reactive hyperplasia secondary to the tumour, or metastatic disease. Occasionally, a 'positive' lymph node is detected in the absence of any obvious primary tumour.
- Second primary neoplasms in the aerodigestive tract may be seen in those with OSCC over 3 years in up to 25%, and in up to 40% of those who continue to smoke.
- Most oral cancer is carcinoma on the lower lip; the other main site is the posterolateral border/ventrum of the tongue.

Clinical features of lip cancer

- In the developed world, nearly 30% of all oral cancer affects the lip: in some ways this can be regarded as a somewhat different disease to intraoral carcinoma.
- Lip cancer affects mainly the lower lip and has a far better prognosis than intraoral cancers.

Clinical features of intraoral cancer

- Some 25% of OSCC in the developed world affects the tongue, the common intraoral site.

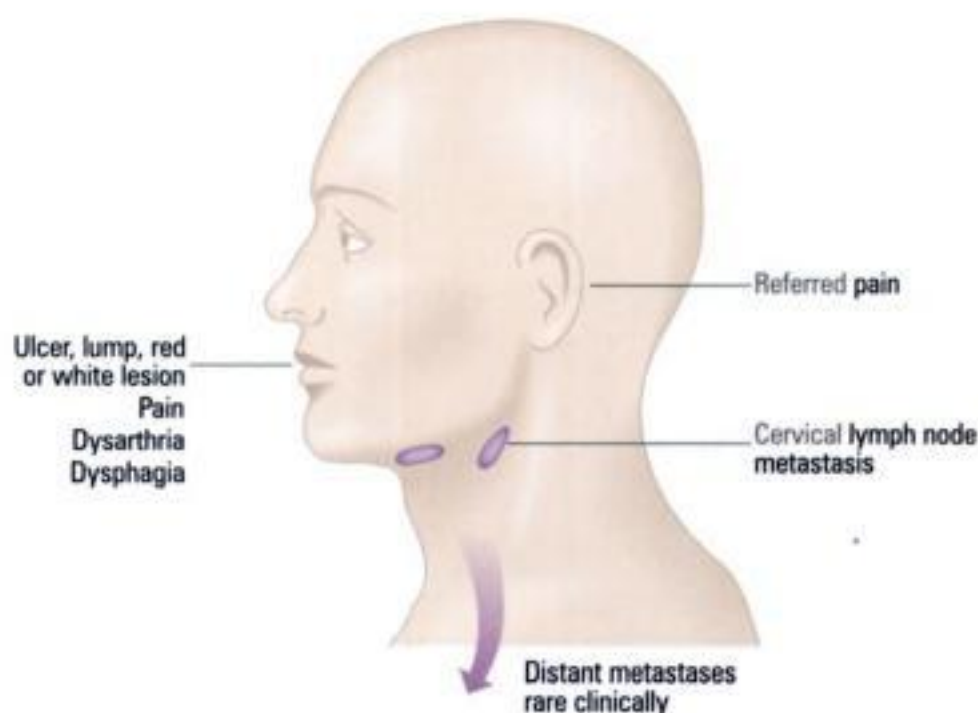


Figure 20.3 Presenting features of oral carcinoma

- The majority of OSCC involve the lateral border of the tongue and/or the floor of the mouth, but the very invasive nature of these tumours makes difficult the precise definition of the site of origin. Nevertheless, most arise from the lower part of the mouth (Table 20.5) raising questions as to why this site appears predisposed to tumour development. Perhaps carcinogens pool in saliva in this so-called 'graveyard' or 'coffin' area?
- In the developing world, where OSCC arises mainly from betel use, OSCC is most common in the buccal mucosa.
- Most intraoral tumours are larger than 2 cm in diameter at presentation.
- Carcinomas in the anterior mouth are usually detected at an earlier stage than are carcinomas of the posterior oral cavity.

Diagnosis

- There should be a high index of suspicion, especially of a solitary lesion present for over 3 weeks: biopsy is invariably indicated. Clinicians should be aware that single ulcers, lumps, red patches or white patches, particularly if any of these are persisting for more than 3 weeks, may be manifestations of frank malignancy.
- The whole oral mucosa should be examined as there may be widespread dysplastic mucosa ('field change') or even a second neoplasm, and the cervical lymph nodes must be examined. Frank tumours should be inspected and palpated to determine the extent of spread; for tumours in the posterior tongue, examination under general anaesthetic may facilitate this.
- OSCC should be staged according to the TNM (Tumour, Node, Metastases) classification of the International Union against Cancer – according to tumour size, nodal metastases and distant metastases (Table 20.6) – since this classification relates well to overall survival rate (i.e. the earlier the tumour, the better the prognosis and the less complicated is the treatment).

Table 20.5 Frequency of carcinoma at different sites

Location	Approx. % of all OSCC	Approx. % of intraoral OSCC
Lip	30	–
Tongue	25	45
Soft palate/trigone area	15	30
Hard palate	5	10
Gingiva	5	10
Buccal mucosa	2	5

Investigations

When deciding which investigations to undertake, three principles should be adhered to:

- Confirm the diagnosis histopathologically, and determine if there is malignant disease elsewhere, whether there are:
 - Bone, muscles or cervical lymph nodes involved.
 - Other primary tumours (typically in the upper aerodigestive tract – mouth, nares, pharynx, larynx, oesophagus). There is controversy as

Table 20.6 TNM classification of malignant neoplasms*

Primary tumour size (T)	
Tx	No available information
T0	No evidence of primary tumour
Tis	Only carcinoma in situ
T1, T2, T3, T4	Increasing size of tumour†
Regional lymph node involvement (N)	
Nx	Nodes could not be or were not assessed
N0	No clinically positive nodes
N1	Single clinically positive homolateral node less than 3 cm in diameter
N2	Single clinically positive homolateral node 3-6 cm in diameter, or multiple clinically positive homolateral nodes, none more than 6 cm in diameter
N2a	Single clinically positive homolateral node 3-6 cm in diameter
N2b	Multiple clinically positive homolateral nodes, none more than 6 cm in diameter
N3	Massive homolateral node(s), bilateral nodes or contralateral node(s)
N3a	Clinically positive homolateral node(s), one more than 6 cm in diameter
N3b	Bilateral clinically positive nodes
N3c	Contralateral clinically positive node(s)
Involvement by distant metastases (M)	
Mx	Distant metastasis was not assessed
M0	No evidence of distant metastasis
M1, M2, M3	Distant metastasis is present. Increasing degrees of metastatic involvement, including distant nodes

*Several other classifications are available, e.g. STNM (S = site)
†T1, maximum diameter 2 cm; T2, maximum diameter 4 cm; T3, maximum diameter >4 cm; T4, massive tumour >4 cm diameter, with involvement of antrum, pterygoid muscles, base of tongue or skin

to the need for endoscopy in all cases to detect such tumours.

Metastases, which initially are to regional lymph nodes and later to liver, bone and brain. Imaging may detect abnormalities that escape clinical examination.

- Ensure that the patient is as prepared as possible for the major surgery required, particularly in terms of their understanding and consent, general anaesthesia, potential blood loss and ability to metabolise drugs.
- Address any potential dental or oral problems preoperatively, to avoid later complications such as osteoradionecrosis.

These three principles almost invariably indicate the following investigations:

- Lesional biopsy.
- Biopsy or fine needle aspiration of equivocal neck lymph nodes.
- Jaw radiography (often rotating pantomography), though this is inadequate to exclude bone invasion.
- Chest radiography. This is important as a preanaesthetic check, especially in patients with known pulmonary or airways disease, and to demonstrate metastasis to lungs or hilar lymph nodes, ribs or vertebrae.
- Magnetic resonance imaging (MRI) or computed tomography (CT) of the primary site, of the head and neck, and suspected sites of distant metastases, and MRI scans of the neck to delineate the extent of cervical node metastases. Some units routinely examine the chest and abdomen. MRI is particularly useful to determine:
 - tumour spread
 - bone involvement
 - nodal metastases.
- Electrocardiography.
- Blood tests:
 - full blood picture and haemoglobin
 - blood for grouping and cross-matching
 - urea and electrolytes
 - liver function tests.

In selected cases other investigations may be indicated:

- bronchoscopy, if chest radiography reveals any lesions
- endoscopy of the upper aerodigestive tract, especially if there is a history of tobacco use
- gastroscopy, if a PEG (perendoscopic gastrostomy) is to be used for feeding
- liver ultrasound, if there is hepatomegaly or abnormal liver function
- Doppler duplex flow studies, in planning radial free forearm flaps
- angiography, in planning lower limb free flaps.

Molecular and DNA techniques are being introduced for prognostication in potentially malignant lesions and tumours, and to identify nodal metastases. Bacteriological investigations may be indicated.

Biopsy

An incisional biopsy is invariably required. The biopsy should be sufficiently large to include enough suspect and apparently normal tissue to give the pathologist a chance to make a diagnosis and not to have to request a further specimen. Most patients tolerate (physically and psychologically) one biopsy session, although it is never a particularly pleasant experience. Most biopsy wounds, whether 0.5 cm (too small) or 1.5 cm long (usually adequate) heal within 7–10 days. Therefore it is better to take at least one ample specimen. Since red rather than white areas are most likely to show dysplasia, a biopsy should be taken of the former. If the pathology report denies malignancy, and yet clinically cancer is still the diagnosis, then the pathology should be re-checked and a re-biopsy may be indicated. Some authorities always take several biopsies at the first visit in order to avoid the delay and aggravation resulting from a negative pathology report in a patient who is strongly suspected to be suffering from a malignant neoplasm.

Various attempts to clinically highlight probably dysplastic areas before biopsy (e.g. by the use of toluidine blue dye or fluorescence) have, unfortunately, not always proven to be reliable, but may be of some help where there is widespread 'field change'.

An excisional biopsy should be avoided, since this is unlikely to have excised an adequately wide margin of tissue if the lesion is malignant, but will have destroyed clinical evidence of the site and character of the lesion.

Suspect lymph nodes are best biopsied by needle biopsy, using a fine-bore needle to aspirate cells for cytological examination. False-negative results are possible, but the danger of incisional biopsy is that it may seed malignant cells into the wound. In practical terms ipsilateral enlarged regional lymph nodes in a patient with an obvious oral carcinoma are likely to include metastases (or at least micrometastases) and will need treatment.

Carcinoma is diagnosed when there is:

- dysplasia extending through the full thickness of the epithelium
- extension of the rete pegs into the underlying lamina propria (i.e. invasion across the basement membrane).

It is generally accepted that prognosis is best in early carcinomas, especially those that are well differentiated (Table 20.7); fortunately, most OSCC is well or moderately differentiated.

Table 20.7 Grades of carcinoma

Carcinoma	Histopathological features
Well-differentiated	Elongated rete pegs invading lamina propria, with keratin pearls
Moderately differentiated	Irregular invading rete pegs; loss of cellular cohesion
Poorly differentiated	Sheets of invading epithelium with no obvious architecture, but severe cellular abnormalities such as pleomorphism and hyperchromatism

Management

Patient communication

Patient communication and information are important aspects in management. One of the most difficult clinical situations in which clinicians find themselves is with the patient in whom serious disease such as cancer is suspected. If the patient is to be referred for a diagnosis and insists (rightly) on a full explanation as to why you need to refer for a second opinion, it is unwise for you to suggest a serious diagnosis to the patient. Better that you admit ignorance about the field and say that you are trained more to be suspicious but doubt the lesion is anything to worry about, though you would be failing in your duty if you did not ask for a second opinion. That is what you would do for a member of your family – why should the patient be treated any the less? Cancer to many, if not most, patients is a term that forebodes disaster – not unreasonably, since most have had relatives or friends who have died of the disease. The prognosis, at least of intraoral carcinoma, is not especially good, but little is gained by expressing this to the patient or relative. On the other hand, early lesions in otherwise healthy patients, especially those in sites such as the lip, have such a good prognosis that they can be said to be 'curable'. You must leave discussion of actual treatment and prognosis to the surgeon/oncologist concerned, as only they are in a position to give accurate facts to the patient concerned. If you are concerned, phone a specialist or e-mail or write for an urgent opinion.

If a cancer diagnosis has been established, it is reasonable to discuss with the patient, their partner and relatives that:

- tumours differ in their degree of malignancy
- their tumour has been detected at an early stage (hopefully)
- treatment is continually improving
- you have referred them to the best possible centre for treatment
- the oncological team will provide fuller details of treatment options.

Treatment planning

Cancer treatment and planning (see Ch. 39) involves a team that includes a range of specialties: surgeons, anaesthetists, oncologists, nursing staff, dental staff, nutritionists, speech and physiotherapists, and others. The oncological team should plan the cancer treatment, but must also plan to avoid postoperative complications – this includes planning oral and dental care. Discussions regarding restorative and surgical interventions required before cancer treatment, including osseointegrated implants and jaw reconstruction, are valuable in the planning phase. Oral care is especially important when radiotherapy is to be given, since there is a liability particularly to mucositis, xerostomia and other complications (see Ch. 39), and a risk of osteonecrosis – the initiating factor for which is often trauma, such as tooth extraction, or ulceration from an appliance, or oral infection. As much as possible of this treatment should be completed before starting cancer treatment.

Treatment modalities

- OSCC is now treated largely by surgery and/or radiotherapy to control the primary tumour and metastases in the draining cervical lymph nodes. Consensus guidelines to treatment are now being published. Combined clinics are needed to agree treatment policy, and offer the best outcomes. Treatment should be planned with a balance in mind between:
 - length of survival
 - quality of remaining life.
- Lip cancer is treated mainly surgically.
- Intraoral cancers <4 cm in diameter may be treated equally effectively by surgery or radiotherapy. For many patients, the treatment must include treatment of the lymph nodes in the neck and thus often the treatment of choice is surgery (tumour excision with radical neck dissection), together with postoperative radiotherapy if there is extracapsular spread or multiple lymph node involvement.

Surgery

Principles

The principles of cancer surgery are to:

- Remove the whole tumour:
 - Ablative surgery excises the cancer with at least a 2 cm margin of clinically normal tissue, to try and ensure no tumour remains.
 - Radical neck dissection, for the same reason, removes also the internal jugular vein, lymphatics and accessory nerve, as well as the cervical sensory nerves and the sternomastoid, omohyoid and often digastric muscles. 'Functional' neck dissection, preserving such vital

structures is gaining popularity; moderate-dose radiotherapy is therefore sometimes used to 'sterilise' such necks of residual cancer cells.

- Retain as much normal anatomy and function as possible.
- Reconstruct to produce acceptable function and cosmetics.

Reconstruction from both the operator's and the patient's and family's viewpoint, is best performed at the time of initial surgery, but must be tailored to the patient's ability to cope with a long operation (up to 10 hours or more) and the risk of significant morbidity. For soft tissue reconstruction, local flaps (e.g. nasolabial flaps) can repair small defects. Distant flaps are required to repair larger defects; these include:

- Free flaps: microvascular surgery facilitates excellent reconstruction at a single operation using, for example, forearm flaps based on radial vessels which are particularly useful to replace soft tissue, or those based on the fibula where bone is required.
- Pedicle flaps: myocutaneous or osteomyocutaneous flaps based on a feeding vessel to muscle and perforators to the skin paddle, for example flaps based on the pectoralis major, latissimus dorsi or trapezius are now used in a one-stage operation to replace skin and, since they also contain muscle, they have adequate bulk to repair defects and may also be used to import bone (usually rib).
- Hard tissue: mandibular defects are reconstructed with implants to maintain aesthetics and anatomy temporarily until the patient is tumour free and bone grafting possible. Bone is traditionally taken as free non-vascularised bone grafts from the iliac crest or rib, but these often show poor survival in a contaminated area like the mouth, or in a relatively avascular field after irradiation. An osteomyocutaneous flap, such as a fibula graft, greatly improves the vascular bed for the graft, but is time consuming and requires considerable expertise. Maxillary defects are reconstructed with an obturator (bung), which has the advantage that the cavity can be readily inspected.

Surgical complications

- Carotid artery infection and rupture.
- Salivary fistula.
- Chylorrhoea.

Advantages and disadvantages of surgery

Advantages of surgery include the possibilities of:

- complete tumour and lymph node excision with full histological examination
- removal of involved bone
- use for radio-resistant tumours.

Disadvantages of surgery are mainly that it is mutilating for very large tumours and there is, in any event, perioperative mortality and morbidity, but modern techniques have significantly decreased these and the aesthetic and functional defects.

Radiotherapy

Principles

Radiotherapy may be used as the sole treatment modality for primary oral cancers without obvious lymph node involvement and also for inoperable tumours.

Radiotherapy can be given by different techniques:

- Interstitial therapy (brachytherapy) is suitable only for small tumours less than 2 cm in size and certain sites. Implants of iridium-192 implanted into the lesion for a few days give a radiation dose equivalent to that from teletherapy, but confined to the lesion and immediate area.
- External beam radiation (teletherapy), which is accompanied more commonly than is brachytherapy by side-effects.

Advantages and disadvantages of radiotherapy

Advantages of radiotherapy include the facts that:

- normal anatomy and function are maintained
- general anaesthesia is not needed
- salvage surgery is still available if radiotherapy fails.

Disadvantages of radiotherapy may include mainly that:

- subsequent surgery is more difficult and hazardous and survival further reduced
- cure is uncommon for large tumours
- adverse effects are common (see Ch. 39).

Rehabilitation

Cancer patients are typically concerned primarily with ridding themselves of the tumour, but aesthetics and restoration of dignity and function are also very important. Feeding can be a problem and it may be necessary to feed via perendoscopic gastrostomy or an indwelling central venous (Hickmann) line. Attention is also required to speech, swallowing, oral hygiene and appearance, with prostheses, implants or camouflage in some cases. Physiotherapy is often required.

Prognosis of intraoral carcinoma

Intraoral cancer should be one of the most readily detected neoplasms because of the easy access for clinical and biopsy examination, yet the

prognosis is still little better than for lung cancer, i.e. an overall 5-year survival of only about 30%.

Factors influencing prognosis include:

- Tumour factors:
 - Increasing stage, depth of infiltration, size of tumour and presence of metastases adversely affect prognosis. Thus the prognosis for stage I tumours is around 85% 5-year survival, but this figure plummets to 10% in stage IV tumours (Table 20.8). Patients still present for treatment after inordinate delays. Most present at a stage (stage II) when tumours are relatively advanced in size (T2 or more, see Table 20.6), but when there is little clinical evidence of loc

and medical care. Apart from the general improved expertise of surgical, anaesthetic and medical care, reconstructive surgery and radiotherapy techniques and after-care have been significantly improved.

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is not a common tumour in Europe or the USA.

- NPC is prevalent in Chinese, North Africans and Inuits.
- It is almost certainly caused by Epstein–Barr virus and other cofactors (environmental and genetic), possibly nitrosamines from smoked fish.
- The tumour usually starts high in the nasopharynx and, because it does not occlude the pharynx to produce symptoms and is very inaccessible to casual inspection, frequently presents late and with a poor prognosis.
- The tumour usually presents in one or a combination of the following ways:
 - Causing unilateral loss of hearing on the same side (ipsilateral) by invading and blocking the eustachian tube. This causes pain, paraesthesiae, or sensory loss in the ipsilateral face – by infiltrating the mandibular division of the trigeminal nerve (Trotter syndrome).
 - With cervical lymph node enlargement due to metastases. NPC is a common cause of a malignant cervical lymph node where no primary tumour is obvious, and therefore a node biopsy and thorough ear, nose and throat examination and biopsy of the fossa of Rosenmuller are required.

Websites

<http://www.entnet.org/cancer.html>

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<http://www.oralcancer.org>

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Candidiasis

Introduction

- *Candida* typically colonises mucocutaneous surfaces but these can be portals for entry into deeper tissues when host defences are compromised.
- The importance of *Candida* has increased greatly, particularly as the HIV pandemic extends.
- *Candida albicans* is the only common cause of oral fungal or yeast infection.
- The most dominant oral species, in decreasing order of frequency, are:
 - *C. albicans*
 - *Candida tropicalis*
 - *Candida glabrata*
 - *Candida parapsilosis*
 - *Candida krusei*
 - other *Candida* species
 - other genera which are rare and transient.
- Species other than *C. albicans* (especially *C. krusei*) are increasingly seen in infections, especially in persons with compromised immunity.
- Antifungal resistance is an increasingly serious clinical reality.

Candida carriage

- Some 50% of the normal population harbour (carry) *C. albicans* as a normal oral commensal and are termed '*Candida* carriers'.
- *C. albicans* resides particularly on the posterior dorsum of tongue.
- *Candida* carriage is more frequent in:
 - women
 - persons of blood group O and with non-secretion of blood group antigens in saliva

- high carbohydrate diets causing acidic saliva
- xerostomia
- broad-spectrum antimicrobial use (e.g. tetracyclines)
- denture wearers
- smokers
- immunocompromised persons such as those with HIV disease, malignancy, Down syndrome, malnutrition or diabetes
- hospitalised patients.

Candida serotypes

C. albicans can be differentiated serologically into A and B serotypes, equally distributed in healthy individuals, but there is a significant shift to type B in immunocompromised patients.

Host defences

The host defences against *Candida* species include:

- Oral epithelium: a physical barrier.
- Microbial interactions: competition and inhibition by the oral flora.
- Salivary non-immune defences: mechanical cleansing plays a major role. Other factors include:
 - lysozyme (muramidase) can damage *Candida*, stimulate phagocytosis and agglutinate *Candida*
 - lactoferrin is antifungal and antibacterial due to binding of iron or altering yeast cell wall permeability
 - lactoperoxidase is anticandidal via multiple factors (H_2O_2 and halides)
 - salivary glycoproteins antigenically similar to blood group antigens affect adherence to mucosa
 - salivary histatins
 - antileukoprotease
 - salivary histidine-rich polypeptides
 - calprotectin.
- Immune defences, which include:
 - T cells and phagocytes are crucial. Polymorphonuclear leukocytes (PMNL) and macrophages phagocytose and produce cytokines such as: myeloperoxidase, tumour necrosis factor (TNF), interferon- γ (IFN- γ), nitric oxide and granulocyte-macrophage colony stimulating factor (GM-CSF).
 - The full expression of phagocyte effectiveness is dependent on augmentation by cytokines synthesised or induced by T cells, such as lymphokines and IFN- γ .
- Salivary sIgA antibodies aggregate organisms and/or prevent adherence.

Pathogenicity

PDFFREE COMUNIDAD ODONTOLÓGICA

Factors implicated in candidal pathogenesis, include:

- **Enzymes:**
 - phospholipases
 - lysophospholipases
 - aspartyl proteinases (secretory aspartyl proteinases (SAP))
 - activating the kallikrein-kinin system.
- Cell-wall mannans and glycans, which may impair PMNL chemotaxis, phagocytosis, respiratory burst, T lymphocyte reactivity and the macrophage secretion of TNF
- Adherence ability: extracellular polymeric material, including mannoprotein and adhesins originating from the yeast cell surface, appears important in making hyphal forms adhere more strongly than yeast forms.
- Colony switching; *C. albicans* can switch frequently and reversibly between several variant, heritable, phenotypes associated with changes in micromorphology, physiology and virulence.

Candidiasis

Candidiasis (candidosis) is the state when *C. albicans* causes lesions.

Symptomatic candidiasis presents as mainly:

- white lesions (thrush, candidal leukoplakia and chronic mucocutaneous candidiasis), in which hyphal forms are common
- red lesions (denture-related stomatitis, median rhomboid glossitis, erythematous candidiasis), in which yeast forms predominate, and which may be symptomless, although antibiotic stomatitis and angular cheilitis can cause soreness.

Factors that can increase the liability to candidiasis include (Table 21.1):

- Local factors influencing oral immunity or ecology, including:
 - xerostomia
 - smoking
 - corticosteroids
 - broad-spectrum antimicrobials
 - cytotoxic chemotherapeutic agents
 - irradiation involving the mouth or the salivary glands
 - malnutrition
 - dental appliances.
- Systemic immune defects, such as those caused by:
 - malnutrition
 - cytotoxic chemotherapy

Table 21.1 Factors predisposing to oral candidiasis

- Disturbed oral ecology or marked changes in the oral microbial flora by antibiotics, corticosteroids, xerostomia, dental appliances
- Immune defects
- Diabetes mellitus
- Malignant and chronic diseases
- Severe blood dyscrasias
- Radiation to the head and neck
- Chemotherapy
- Hospitalisation
- Heavy smoking
- Malnutrition and dietary factors
- Extremes of age

- immunosuppressant drugs, such as corticosteroids
- T-cell defects, especially HIV infection, leukaemias, lymphomas and cancer
- PMNL defects, such as in diabetes
- anaemia.

Classifications

By tradition, the most frequently adopted classification of oral candidiasis has been into (Table 21.2):

- Acute candidiasis:
 - pseudomembranous candidiasis (thrush)
 - atrophic candidiasis.
- Chronic candidiasis:
 - hyperplastic candidiasis
 - atrophic candidiasis
 - hyperplastic candidiasis, which was further subdivided into four groups based on localisation patterns and endocrine involvement as follows: chronic oral candidiasis (*Candida* leukoplakia); candidiasis endocrinopathy syndrome; chronic localised mucocutaneous candidiasis; and chronic diffuse candidiasis.

A newer classification categorises candidiasis into:

- primary oral candidiasis, which is confined to oral and perioral tissues
- secondary oral candidiasis, which is distributed in other parts of the body as well as the oral cavity.

Table 21.2 Classification of oral candidiasis**Primary oral candidiasis (group I)**

- Acute: pseudomembranous, erythematous
- Chronic: pseudomembranous, erythematous
- *Candida*-associated lesions

Secondary oral candidiasis (group II)

- Oral manifestations of systemic mucocutaneous candidiasis (due to diseases such as thymic aplasia and candidiasis endocrinopathy syndrome)
- Hyperplastic plaque-like, nodular
- Denture-related stomatitis, angular stomatitis, median rhomboid glossitis

Diagnosis of candidiasis

Diagnosis can, if necessary, be supported by:

- identification of blastospores and pseudohyphae in stained smears from a lesion
- culture, usually on Sabouraud's or dextrose Sabouraud's medium
- occasionally by histology stained by periodic acid Schiff (PAS).

However, the diagnosis of candidiasis in most instances is clinical and investigations can be complicated by the facts that:

- up to about 50% of the population are carriers
- any attempt at quantitation of *Candida* is affected by time of sampling and the way in which the specimen is handled.

See the relevant clinical presentations described below.

Other investigations

- Tests of immune function are indicated mainly in HIV disease or chronic mucocutaneous candidiasis.
- Since some endocrine disorders may be associated with chronic mucocutaneous candidiasis, tests of thyroid or adrenocortical function are warranted in selected individuals.
- Since oral candidiasis is occasionally associated with nutritional deficiencies or blood dyscrasias, estimates of haemoglobin, white blood cell counts, corrected whole blood folate, vitamin B₁₂ and serum ferritin can be important.

Management of candidiasis

Few patients have spontaneous remission unless the condition is solely related to, for example, the use of an antimicrobial, or a topical corticosteroid, and thus, in other cases, treatment is often indicated. Often, in the treatment of fungal infection, attention to the underlying cause will avoid the need for prolonged or repeated courses of treatment. Intermittent or prolonged topical antifungal treatment may be necessary where the underlying cause is unavoidable or incurable.

Treatment includes the following measures:

- Avoid or reduce smoking.
- Treat any local predisposing cause such as xerostomia.
- Improve oral hygiene; chlorhexidine has some anti-candidal activity.
- Antifungals:
 - Topical antifungal agents are useful for most lesions restricted to the oral cavity and are available as suspensions, tablets and creams. Oral suspensions are useful for patients with dry mouth who may have difficulty in dissolving tablets. Available preparations include: nystatin oral suspension or pastilles, amphotericin lozenges, miconazole gel or tablets, fluconazole tablets or suspension.
 - Systemic antifungals are increasingly used, especially fluconazole, but may interact with anti-HIV and other medications.

See the relevant clinical presentations described below.

Prophylaxis of candidiasis

- In patients with severe immunosuppression, prevention of colonisation and infection is the goal because the oropharyngeal region may be the primary source of initial colonisation and allow subsequent spread of the infection.
- Those at greatest need for such prophylactic antifungals include patients:
 - with HIV disease
 - receiving cancer chemotherapy
 - on immunosuppressive therapy
 - on prolonged antibiotic therapy.

Clinical presentations of candidiasis

The most common form of oral candidiasis is denture-related stomatitis, and sometimes this is complicated by angular stomatitis, again often a

Candida-related lesion. Thrush is not uncommon in neonates, as they have yet to develop acquired immunity, but was rare in older persons before the advent of immunosuppressive therapies and HIV/AIDS. The latter has also highlighted the other red, or erythematous, forms of oral candidiasis. The various types are now discussed in more detail.

Denture-related stomatitis

Denture-related stomatitis is discussed in Chapter 22.

Angular stomatitis

Angular stomatitis (perleche, angular cheilitis) is discussed in Chapter 14.

Thrush

Thrush is the common title for acute pseudomembranous candidiasis, and is so termed because the white flecks resemble the appearance of the breast of the bird of that name.

Incidence

Uncommon in healthy individuals but common in immunocompromised persons.

Age

Can occur at any age.

Sex

It can occur in either sex.

Geographic

Candidiasis is seen worldwide.

Predisposing factors

Predisposing factors include changes in local or systemic immunity in the mouth. Thrush in most patients is related to antibiotic or corticosteroid use, or xerostomia. However, if these local factors cannot be identified, systemic disease should be suspected.

Neonates, who have yet to develop immunity to *Candida* species, may also develop thrush.

Thrush is importantly a 'disease of the diseased' seen mainly in patients with immune defects such as terminally ill patients particularly in association with serious underlying conditions, such as leukaemia and other malignancies, and in HIV disease and patients on immunosuppressive medication.

Aetiology and pathogenesis

- Thrush is mainly caused by *C. albicans*. In infant thrush, *C. parapsilosis* is frequently found.
- With the increasing use of antimycotic therapy, especially in HIV disease, there is a shift towards not only antifungal-resistant *C. albicans*, as well as the appearance of novel species such as *C. dubliniensis*, but also towards other species such as *C. glabrata* and *C. krusei*.
- *C. albicans* adhere to the epithelial surface via extracellular polymeric material, including mannoprotein and adhesions.
- *C. albicans* hyphae invade the superficial epithelium and penetrate by liberation of enzymes such as phospholipases, lysophospholipases and aspartyl proteinase, as far as the stratum spinosum. PMNL migrate into the epithelium in defensive mode, but candidal cell-wall mannans and glycans may impair PMNL chemotaxis, phagocytosis and respiratory burst. Oedema and micro-abscesses containing PMNL are found in the outer layers of epithelium. The deeper parts of the epithelium show acanthosis and sometimes even dysplasia.
- Activation of the kallikrein-kinin system and other factors result in an inflammatory response in the connective tissue comprising lymphocytes, plasma cells and PMNL.
- The plaques in oral thrush are made up of necrotic material, *Candida* and desquamated parakeratotic epithelia.

Clinical features

Thrush is classically an acute infection, but it may persist for many months or even years in patients using corticosteroids topically or by aerosol, in HIV-infected individuals, and in other immunocompromised patients.

Thrush is characterised by:

- White papules on the surface of the oral mucosa. These may form confluent plaques that resemble milk curds (Fig. 21.1). These can be wiped off with gauze to reveal a raw, erythematous and sometimes bleeding base.
- Complications, which may sometimes be lesions of the mucosa of the upper respiratory tract and the oesophagus, a combination particularly prevalent in HIV-infected patients.

Diagnosis

The diagnosis of thrush is usually clinical and straightforward, but it has been overdiagnosed in the past. In immunosuppressed patients, a Gram-stained smear should be taken to distinguish it from the thrush-like plaques produced by opportunistic bacteria. Hyphae seem to indicate that the *Candida* are acting as pathogens.



Figure 21.1 Thrush showing white and red lesions

Management

Possible predisposing causes should be looked for and dealt with, if possible. Topical polyene antifungals such as nystatin or amphotericin, or imidazoles such as miconazole or fluconazole are often indicated.

Chronic hyperplastic candidiasis

Chronic hyperplastic candidiasis, or candidal leukoplakia is a persistent white lesion, characterised histologically by parakeratosis and chronic intraepithelial inflammation with fungal hyphae invading the superficial layers of the epithelium.

Incidence

It is uncommon.

Age

It is found in adults.

Sex

It can occur in either sex.

Geographic

It can be found worldwide.

Predisposing factors, aetiology and pathogenesis

- The epithelium of some leukoplakias is invaded by *Candida* hyphae, but it is unclear whether the yeasts are secondary invaders or are causally involved in the development or transformation of leukoplakia.

- The cellular changes often include hyperplasia, but cellular atypia, mild or severe dysplasia and ultimately in situ or invasive carcinoma may arise.
- *C. albicans* is the species by far the most commonly isolated.
- However, the *Candida* biotypes associated with leukoplakias differ from those isolated from normal oral cavities.
- Also, the *Candida* types from non-homogeneous leukoplakias such as candidal leukoplakia have higher nitrosation potentials than others, which might indicate a possible role of specific types in the malignant transformation of some leukoplakias.
- Candidal leukoplakia may be predisposed to in a minority of patients by:
 - smoking
 - iron and folate deficiencies
 - defective cell-mediated immunity
 - blood group secretor status.

Clinical features

- Candidal leukoplakias are chronic, discrete raised lesions that vary from small, palpable, translucent, whitish areas to large, dense, opaque plaques, hard and rough to the touch (plaque-like lesions). Homogeneous areas or speckled areas can be seen, which do not rub off (nodular lesions).
- Candidal leukoplakias are non-homogeneous 'speckled' leukoplakias in up to 50%.
- Candidal leukoplakias usually occur on the buccal mucosa on one or both sides, mainly just inside the commissure, less often on the tongue.

Diagnosis

Candidal leukoplakias can be indistinguishable from other leukoplakias except by biopsy when *Candida* hyphae can be seen after staining with periodic acid Schiff (PAS). Candidal leukoplakia should therefore be biopsied both to:

- distinguish it from other non-candidal lesions
- examine for possible dysplasia.

Management

From 9% to 40% of candidal leukoplakias may develop into carcinomas.

Factors influencing the prognosis may include:

- risk factors, such as tobacco and alcohol use
- whether the lesion is speckled (more dangerous) or homogeneous
- the presence (more dangerous) and degree of epithelial dysplasia
- the management adopted.

In order to improve the prognosis:

- Tobacco and alcohol habits should be stopped.
- Antifungals should be used. The lesions of candidal leukoplakia may prove poorly responsive to polyene antifungal drugs and, in some cases, respond only to systemic fluconazole.
- Excision is indicated if there is more than mild dysplasia.
- The patient should be fully informed about the condition, and reviewed regularly.

Chronic mucocutaneous candidiasis

Chronic mucocutaneous candidiasis (CMC) is the term given to the group of rare syndromes in which there is persistent mucocutaneous candidiasis that responds poorly to topical treatment. Specialist care is indicated (Table 21.3).

- Chronic mucocutaneous candidiasis syndromes are sometimes familial and present early in life, and one type (candidiasis endocrinopathy syndrome) is associated with autoimmune endocrinopathies, especially hypoparathyroidism, and hypoadrenocorticism (polyendocrinopathy syndrome type I).
- In many patients with persistent oral candidiasis no local cause or underlying defect can be identified.
- In general, the more severe the candidiasis and the more widespread the sites involved, the greater is the likelihood that an immunological defect (particularly of cell-mediated immunity) can be identified.

Table 21.3 Chronic mucocutaneous candidiasis		
Type	Inheritance	Clinical features
Localised CMC	Sporadic	Persistent oral candidiasis, oesophagitis, iron deficiency
Diffuse CMC (<i>Candida</i> granuloma)	AR or sporadic	Severe chronic oral candidiasis, granulomas, susceptibility to bacterial infections
Candidiasis–endocrinopathy syndrome	AR	Mild chronic oral candidiasis, pernicious anaemia, hypoparathyroidism, hypoadrenocorticism, diabetes, vitiligo, thyroid disease
Candidiasis thymoma syndrome	Sporadic	Chronic oral candidiasis, myasthenia gravis, polymyositis, aplastic anaemia

- A defect of cytokine production (interleukin-2 and IFN- γ) in response to candidal and some bacterial antigens, with reduced Th1 lymphocyte function and enhanced Th2 activity (and increased interleukin-6), and reduced serum levels of IgG2 and IgG4 may be found in some patients.

Erythematous candidiasis

Erythematous or atrophic candidiasis is candidiasis presenting as red lesions. Red lesions may be seen in denture-related stomatitis, antibiotic-induced stomatitis, sometimes in median rhomboid glossitis and, in HIV infection, may develop *de novo*, may precede pseudomembranous candidiasis, or may arise as a consequence of persistent acute pseudomembranous candidiasis when the pseudomembranes are shed.

Denture-related stomatitis

Denture-related stomatitis (denture sore mouth; chronic atrophic candidiasis) consists of mild inflammation of the mucosa beneath a denture, usually a complete upper denture (see Figs 22.1 and 22.2; discussed in Chapter 22).

Antibiotic or steroid-induced stomatitis

Incidence

It is uncommon.

Age

It can occur at any age.

Sex

It can occur in either sex.

Geographic

It has no known geographic incidence.

Predisposing factors

Acute oral candidiasis may complicate corticosteroid or antibiotic therapy, particularly with long-term, broad-spectrum antimicrobials such as tetracycline.

Clinical features

There is widespread erythema and soreness of the oral mucosa, sometimes with thrush.

Diagnosis

This is a clinical diagnosis, but if the aetiology is not absolutely clear a blood picture and smears for fungal hyphae and culture may be helpful management.

Management

- The causal drug should be stopped if possible.
- Tobacco habits should be stopped.
- Antifungals are indicated. However, the lesions may prove poorly responsive to the polyene antifungal drugs and therefore an azole is preferred. Some cases respond only to systemic fluconazole.

Median rhomboid glossitis

Median rhomboid glossitis (MRG), or glossal central papillary atrophy, is a depapillated rhomboidal area in the centre line of the dorsum of the tongue, just anterior to the sulcus terminalis.

Incidence

It is uncommon.

Age

It can occur at any age.

Sex

It can occur in either sex.

Geographic

It has no known geographic incidence.

Predisposing factors

Candida species colonise mainly the posterior dorsum of the tongue, even in healthy patients, but MRG is predisposed by:

- smoking
- denture wearing
- corticosteroid sprays/inhalers
- HIV infection.

Aetiology and pathogenesis

Formerly thought to be caused by persistence of the tuberculum impar, this lesion is now thought to be related to candidiasis because:

- Culture frequently shows *Candida*, although often in a mixed

bacterial/fungal microflora.

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- **Histopathologically**, candidal hyphae infiltrate the superficial layers of the parakeratotic epithelium and a PMNL infiltrate occupies the epithelium, with elongated hyperplastic rete ridges (pseudoepitheliomatous hyperplasia), and a lymphocyte infiltration in the corium. Thus there can be a trap for the unwary, since the lesion may be mistaken for a cancer.

Clinical features

MRG is only rarely sore, but is more usually detected incidentally by the patient or dentist. It is characterised by:

- An area of papillary atrophy which is usually reddish or red and white, or occasionally white. It is elliptical or rhomboidal in shape, symmetrically placed centrally at the midline of the tongue, just anterior to the circumvallate papillae (see Fig. 21.2).
- Occasionally by a hyperplastic, or even lobulated exophytic appearance.

Diagnosis

MRG is usually a clinical diagnosis. Biopsy is rarely indicated; histology shows irregular epithelial hyperplasia, which resembles, but is not, a carcinoma (because of the pseudoepitheliomatous hyperplasia).



Figure 21.2 Median rhomboid glossitis

Rarely, is there a need for blood picture, smears for fungal hyphae or culture.

Management

- Tobacco habits should be stopped.
- Antifungals are indicated. However, the lesions may prove poorly responsive to the polyene antifungal drugs, and some cases respond only to systemic fluconazole.

Erythematous candidiasis in HIV disease

Incidence

It is uncommon.

Age

It can occur at any age.

Sex

It can occur in either sex.

Geographic

It has no known geographic incidence.

Predisposing factors

- The immunological defect.
- Smoking.
- Corticosteroid therapy.
- Broad-spectrum antibiotic therapy.
- Xerostomia (from HIV-salivary gland disease, or some antiretroviral agents which also have this effect).

Clinical features

- The clinical presentation is of irregular erythematous macules and/or patches, generally on the dorsum of the tongue, palate or buccal mucosa.
- Lesions are often seen in the central palate and sometimes termed 'thumbprint lesions'.
- Lesions on the dorsum of the tongue present as glossitis or depapillated areas.
- There can be an associated angular stomatitis.

Diagnosis

This is a clinical diagnosis; biopsy is only rarely indicated. Occasionally there is a need for smears or culture.

Management

- Tobacco habits should be stopped.
- Antiretroviral treatment.
- Since the lesions in HIV disease may prove poorly responsive to the polyene antifungal drugs, systemic fluconazole is usually indicated.

Chronic multifocal oral candidiasis

In a minority of apparently healthy individuals, chronic candidal infection may be seen in multiple oral sites, and this is termed 'chronic multifocal oral candidiasis'. The diagnostic criteria include:

- lesions of more than 1 month duration
- an absence of predisposing medical conditions

It excludes patients who have received radiotherapy or drugs of the following types: antibiotics, anti-inflammatory or immunosuppressive drugs, cytotoxic or psychotropic agents.

Incidence

It is uncommon.

Age

Adults usually; most of the patients are in their fifth or sixth decade.

Sex

Most patients are males.

Geographic

No known geographical incidence.

Predisposing factors

Tobacco smoking is a known risk factor.

Clinical features

Various combinations can be seen, including:

- retrocommissural leukoplakia, which is the most constant component
- angular stomatitis, which is unilateral or bilateral and encountered mainly in denture-wearers
- median rhomboid glossitis
- palatal red irregular patches.

Diagnosis

This is a clinical diagnosis. A blood picture, smears for fungal hyphae and culture may help management.

Management

- Tobacco habits should be stopped.
- Antifungals are indicated. However, the lesions may prove poorly responsive to the polyene antifungal drugs and some cases respond only to systemic fluconazole.

Websites

<http://www.panix.com/lcandida>

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22

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Denture-related

Predisposing factors

- Dental appliance wearing (mainly maxillary dentures), especially when worn throughout the night, or with a dry mouth, is the major predisposing factor.
- Diabetes or a high carbohydrate diet occasionally predispose.
- HIV is a rare underlying factor.
- Factors that are usually *not* significant include:
 - Allergy to the dental material (if it were, denture-related stomatitis would affect mucosae other than just that beneath the appliance).
 - Trauma; the condition is more common beneath maxillary dentures than mandibular dentures, yet trauma is more common under the latter.
 - Pharmacological agents.
 - Smoking.

Aetiology and pathogenesis

- Dentures can produce a number of ecological changes, including:
 - Changes in the oral flora.
 - Plaque accumulation between the mucosal surface of the denture and the palate.
 - Saliva present between the maxillary denture and the mucosa may have a lower pH than usual.
 - The accumulation of microbial plaque (bacteria and/or yeasts) on and in the fitting surface of the denture and the underlying mucosa. In some persons, the cause appears to be related to a non-specific plaque. This plaque undergoes sequential development, and is colonised by *Candida* organisms and, though there is no increased aspartyl proteinase production from the *Candida* involved, the decreased salivary flow and a low pH under the denture probably will result in a high *Candida* enzymatic activity, which can cause inflammation.
- Yeasts, such as *Candida*, are isolated in up to 90% of persons with denture-related stomatitis, but even 66% of denture wearers have them.
- The most frequently isolated organism is *Candida albicans*.
- When *Candida* species are involved in denture-related stomatitis, the more common terms '*Candida*-associated denture stomatitis', 'denture-induced candidiasis' or 'chronic atrophic candidiasis' are used.
- Denture-related stomatitis is not exclusively associated with *Candida* however, and occasionally other factors such as bacterial infection, or mechanical irritation are at play.
- Histological examination of the soft tissue beneath dentures has shown

proliferative or degenerative responses with reduced keratinisation and thinner epithelium.

- However, it not clear why only some denture-wearers develop denture stomatitis, since most patients appear otherwise healthy – and there have been few studies. Patients with denture-related stomatitis have no serious cell-mediated immune defects, but they may sometimes be deficient in migration-inhibition factor (MIF) and may have overactive suppressor T cells or other T lymphocyte or phagocyte defects.

Clinical features

The characteristic presenting features of denture-related stomatitis are:

- chronic erythema and oedema of the mucosa that contacts the fitting surface of the denture, usually a complete upper denture; the mucosa below lower dentures is rarely involved
- erythema restricted to the denture-bearing area (Figs 22.1 and 22.2)



Figure 22.1 Denture-related stomatitis



Figure 22.2 Denture-related stomatitis (denture *in situ*)

- usually no symptoms
- uncommon complications, which include:
 - angular stomatitis
 - papillary hyperplasia in the vault of the palate.

Classification

Denture-related stomatitis has been classified into three clinical types (Newton's types), increasing in severity:

- Type 1: a localised simple inflammation or a pinpoint hyperaemia.
- Type 2: an erythematous or generalised simple type presenting as more diffuse erythema involving a part of, or the entire, denture-covered mucosa.
- Type 3: a granular type (inflammatory papillary hyperplasia) commonly involving the central part of the hard palate and the alveolar ridge.

Diagnosis

- This is a clinical diagnosis.
- Diabetes should be excluded, and a blood picture, smears for fungal hyphae and culture or other investigations such as HIV serology may be indicated if there is angular stomatitis, or other oral or systemic lesions.

Management

- Patient information is probably the most important aspect in management.
- Any underlying systemic disease should be treated where possible.
- The denture plaque and fitting surface is infested, usually with *Candida albicans*, which should be removed.
- Studies of sensitivity to antifungal agents have shown that isolates from different strains are sensitive to amphotericin and nystatin, but less sensitive to miconazole. Fluconazole is as effective as newer agents such as itraconazole. The cyclodextrin solution of itraconazole and capsule preparations of itraconazole are equally effective adjuncts in the treatment but, because of side effects, capsules are preferred. Therefore, to treat and prevent recurrence of denture-related stomatitis:
 - Dentures should be left out of the mouth at night, cleaned and disinfected, and stored in an antiseptic.
 - Denture cleansers can be divided into groups according to their main components: alkaline peroxides, alkaline hypochlorites, acids, yeast

Patient information sheet**DENTURE CARE**

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- If you still have some natural teeth, these will need regular attention, because wearing a denture can encourage food accumulation.
- Keep your dentures as clean as natural teeth. Clean both surfaces of your dentures (inside and outside) after meals and at night. Use washing-up liquid and a tooth brush and lukewarm water and hold it over a basin containing water, in case you drop the denture, which could cause it to break. Never use hot water, as it may alter the denture colour. A disclosing agent, for example Rayner's Blue or red food colouring (available at most supermarkets), can be applied with cotton buds, to help you see whether you are cleaning the denture thoroughly enough. If stains or calculus deposits are difficult to remove, try an overnight immersion (e.g. Dentural, Milton or Steradent) or an application of Denclen.
- Your dentures should be left out overnight, so that your mouth has a rest. It is not natural for your palate to be covered all the time, and the chances of getting an infection are increased if the dentures are worn 24 hours a day. Ensure you leave the dentures out for at least some time and keep them in water, Dentural or Steradent, or in a damp tissue, as they may distort if allowed to dry out.
- Special precautions for dentures with metal parts: Denclen, Dentural and Milton may discolour metal, so use with care. Brush briefly to remove stains and deposits, rinse well with lukewarm water and do not soak overnight in these solutions.
- Before re-use, brush the dentures to remove loosened deposits.

lytic enzymes, proteolytic enzymes and disinfectants such as hypochlorite. Denture soak solutions containing benzoic acid completely eradicate *C. albicans* from the denture surface as it is taken up into the acrylic resin and eliminates the organism from the internal surface of the prosthesis. An oral rinse containing chlorhexidine gluconate also results in complete elimination of the presence of *C. albicans* on the acrylic resin surface of the denture, and in reduction of palatal inflammation. A protease-containing denture soak (alcalase protease) is also an effective way of removing denture plaque, especially when combined with brushing. Hypochlorite is an effective anti-candidal, but can turn chrome cobalt dentures black.

- The mucosal infection is eradicated by brushing the palate and using antifungals for 4 weeks. Effective agents include, nystatin pastilles or

Patient information sheet**DENTURE SORE MOUTH**

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- Denture sore mouth is common but not sore.
- It is caused by a fungus (*Candida*) that usually lives harmlessly in the mouth and elsewhere.
- It is caused mainly by wearing a dental appliance, which allows the fungus to grow.
- It may be precipitated by prolonged appliance-wearing, especially at night.
- It predisposes to sores at the corners of the mouth.
- It has no serious long-term consequences.
- Blood tests, microbiological studies or biopsy may be required.
- It may be controlled by:
 - leaving out the denture, to allow the mouth to heal
 - disinfecting the denture
 - using antifungal creams or gels (e.g. Daktarin) or tablets (e.g. Nystan, Fungilin, Diflucan) regularly for up to 4 weeks.
- The dentures may require adjustment.

suspension, amphotericin lozenges or miconazole gel or fluconazole suspension or tablets, administered concurrently with an oral antiseptic such as chlorhexidine, which has antifungal activity.

- Miconazole lacquer, or antifungals such as fluconazole in tissue conditioners applied to the denture fitting surface are also effective.

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Erythema Migrans

Introduction

Erythema migrans (geographic tongue, benign migratory glossitis) is a common condition, where the tongue has red patches that resemble a map ('geographic' tongue). It has no relationship with erythema migrans of the skin.

Incidence

It occurs in 1–2% of adults and is a common cause of a sore tongue.

Age

It may be seen at any age.

Sex

It can occur in either sex.

Geographic

It has no known geographic incidence.

Predisposing factors

- There is a genetic background; there is:
 - often a family history
 - an increased incidence of HLA-Cw6, DR5 and DRW6 antigens and a decrease in B51 antigen

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Erythema Multiforme

Introduction

Erythema multiforme (EM) is an acute, often recurrent, hypersensitivity reaction affecting mucocutaneous tissues, seen especially in males, and characterised by serosanguinous exudates on the lips, mouth ulceration and sometimes target-like lesions on skin.

Incidence

It is uncommon.

Age

Younger adults (peaks between 20 and 40 years of age) are affected. Twenty per cent of cases occur in children.

Sex

It is more common in males.

Geographic

It is seen worldwide.

Predisposing factors

- A range of usually exogenous factors trigger what appears to be an immunologically-related reaction with sub- and intraepithelial vesiculation.
- There may be a genetic predisposition, with associations of recurrent EM with HLA-B15(B62), HLA-B35, HLA-A33, HLA-DR53 and HLA-DQB1*0301.
- HLA DQ3 has been proven to be especially related to recurrent EM and may be a helpful marker for distinguishing herpes-simplex-associated EM (HAEM) from other diseases with EM-like lesions.
- Patients with extensive mucosal EM may have the rare HLA allele DQB1*0402.

Aetiology and pathogenesis

The aetiology of erythema multiforme (EM) is unclear in most patients, but it appears to be an immunological hypersensitivity reaction with the appearance in the epithelium of cytotoxic effector cells and CD8⁺ T lymphocytes which induce apoptosis of keratinocytes leading to satellite cell necrosis. The reaction is triggered mainly by:

- Infective agents: particularly herpes simplex virus (herpes-associated EM (HAEM)). HSV is implicated in 70% of recurrent EM. Numerous other organisms, particularly mycoplasmas, have also been implicated.
- Immune conditions: such as BCG or hepatitis B immunisation, sarcoidosis, graft-versus-host disease, inflammatory bowel disease, polyarteritis nodosa or systemic lupus erythematosus.
- Food additives or chemicals: such as benzoates, nitrobenzene, perfumes, terpenes.
- Drugs: such as antimicrobials (sulphonamides, e.g. co-trimoxazole), cephalosporins, aminopenicillins, quinolones), barbiturates, non-steroidal anti-inflammatory drugs, anticonvulsants, protease inhibitors and many others may trigger severe EM or, in particular, toxic epidermal necrolysis.

Clinical features

EM may present within a wide spectrum of severity, from mild limited disease (mild EM) to a severe, widespread and life-threatening illness (major EM). Most patients with EM (70%), of either minor or major forms, have oral lesions. Oral involvement may:

- Precede lesions on other stratified squamous epithelia, or may arise in isolation.
- Typically presents with:
 - lesions that progress through diffuse and widespread macules to blisters and ulceration
 - lips that become swollen and cracked, bleeding, and crusted (Fig. 24.1)
 - lesions on the non-keratinised mucosae and most pronounced in the anterior mouth.
- Recur in about 25%. The periodicity can vary from weeks to years; usually attacks last for 10–20 days once or twice a year.
- Resolve after about 6 episodes.

Skin lesions

- Skin lesions commonly affect the distal extremities, especially the extensor surfaces of the arms, legs, elbows, knees, dorsum of hands and feet.
- They are usually macules which are symmetric, round, erythematous and slightly pruritic or non-itchy and may evolve into papules or plaques which frequently display a circumferential pallor and evolve into target or iris lesions.
- Target lesions are large annular (ring-shaped) lesions with concentric rings. The well-demarcated centre of the papule forms a necrotic ulcer, which results in a depressed white, yellow or grey area surrounded by a red edge and then a pale oedematous ring; a bright red margin may surround this pale ring.

Other mucosae

Eye involvement may cause lacrimation and photophobia. Genital lesions are painful and may result in urinary retention.



Figure 24.1 Labial swelling and crusting in erythema multiforme

Forms of EM

The degree of mucosal involvement is the distinguishing feature between minor and major forms.

- Minor erythema multiforme:
 - Affects only one site.
 - May affect the mouth alone, or skin or other mucosae.
 - Rashes are various, but are typically 'iris' or 'target' lesions or bullae on extremities.
- Major erythema multiforme (Stevens-Johnson syndrome (SJS)):
 - Almost invariably involves the oral mucosa.
 - Causes widespread lesions also affecting the eyes, pharynx, larynx, oesophagus, skin and genitals.
 - Begins with a prodrome in about 30% of cases, may begin within 1–3 weeks of starting a new drug, lasts 1–2 weeks before the onset of the mucocutaneous manifestations, and presents with flu-like symptoms, sore throat, headache, arthralgias, myalgias or fever.
 - May present also with bullous and other rashes, pneumonia, arthritis, nephritis or myocarditis. Ocular changes which resemble those of mucous membrane pemphigoid (dry eyes and symblepharon) may result. Balanitis, urethritis and vulval ulcers may occur.
 - Mucosal erosions plus typical or raised atypical targets and epidermal detachment involving less than 10% of the body surface and usually located on the extremities and/or the face characterise HSV-induced EM major.
 - Mucosal erosions plus widespread distribution of flat atypical targets or purpuric macules and epithelial detachment involving less than 10% of body surface on the trunk, face and extremities are characteristic of drug-induced SJS.

Diagnosis

A diagnosis of erythema multiforme can be difficult to readily establish, and there can be a need to differentiate from viral stomatitides, pemphigus, toxic epidermal necrolysis and the subepithelial immune blistering disorders (pemphigoid and others).

- The diagnosis is mainly clinical; the Nikolsky sign is negative.
- It may be helpful to undertake serology for HSV or *Mycoplasma pneumoniae*, or for other micro-organisms.
- Biopsy of perilesional tissue, with histological and immunostaining examination, are essential if a specific diagnosis is required. Biopsy shows:

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Erythroplakia, Leukoplakia, Keratosis and other Potentially Malignant Lesions

Introduction

Most mouth carcinomas appear to arise in apparently normal mucosa, but some are preceded by potentially malignant (sometimes termed *pre-malignant*) clinically obvious lesions, especially:

- erythroplakia (erythroplasia – red patch)
- leukoplakia (white patch) – some, particularly:
 - speckled leukoplakia (red and white patch)
 - verrucous leukoplakia.

Many other cancers are associated with such lesions.

Conditions that may predispose to malignancy include:

- non-reticular lichen planus
- lupus erythematosus
- syphilitic glossitis
- submucous fibrosis
- actinic cheilitis
- previous oral malignancy
- immunosuppression.

Habits that may predispose to malignancy include:

- tobacco use
- alcohol use
- betel nut chewing
- sunlight exposure.

Most potentially malignant lesions show dysplasia on biopsy, and this appears to be the most predictive marker in current use for malignant potential. Features of dysplasia can be seen in Table 25.1.

- *Mild atypia* is the term used where few of the features of dysplasia are present and the epithelium is reasonably well organised.
- *Severe dysplasia* is the term used if organisation is disrupted and many cellular abnormalities present.

Factors predictive of future malignant transformation may include:

- dysplasia
- history of cancer in the upper aerodigestive tract
- P53 tumour suppressor expression
- loss of heterozygosity involving chromosomes 3p or 9p
- chromosomal polysomy (as shown in Table 25.2).

Table 25.1 Features of dysplasia	
Disorderly maturation	Disturbed cell proliferation
● Irregular hyperplasia and/or atrophy	● Loss of basal cell polarity
● Keratosis/parakeratosis	● Basal cell hyperplasia
● Drop-shaped rete processes	● Increased nuclear/cytoplasmic ratio
● Irregular stratification	● Enlarged nucleoli
● Disturbed cell polarity	● Nuclear hyperchromatism
● Cell keratinisation	● Increased mitoses
● Reduced cell cohesion	● Anisonucleosis
● Cell pleomorphism	● Abnormal mitoses

Table 25.2 Potentially malignant lesions: chromosomal polyploidy and prognosis	
DNA content	% transformation in 10 years
Diploid	3
Tetraploid	60
Aneuploid	84
Adapted from Sudbo et al (2001)	

Erythroplakia (erythroplasia)

Erythroplasia is a rare condition defined as 'any lesion of the oral mucosa that presents as bright red velvety plaques which cannot be characterised clinically or pathologically as any other recognisable condition' (WHO, 1978). Erythroplastic lesions are well-defined velvety red plaques which are usually (at least 85%) severely dysplastic or frankly malignant. Erythroplasia is the oral lesion with the most severe dysplasia and greatest predilection to develop to carcinoma.

Incidence

Uncommon: mainly seen in elderly men. It is much less common than leukoplakia.

Age

Occurs in the middle aged and the elderly.

Sex

Occurs mostly in men.

Geographic

It has no known geographic incidence.

Predisposing factors

Unknown, but tobacco and alcohol use are probably involved.

Aetiology and pathogenesis

Erythroplasia contains areas of dysplasia, carcinoma *in situ*, or invasive carcinoma in virtually every case. Carcinomas are seen 17 times more frequently in erythroplakia than in leukoplakia, and these are therefore the most potentially malignant of all oral mucosal lesions, but erythroplasia is far less common than leukoplakia.

Clinical features

Red velvety patch of variable configuration, usually level with or depressed below surrounding mucosa, commonly on:

- soft palate
- floor of mouth
- buccal mucosa (Fig. 25.1).

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- within 1 month
- at 3 months
- at 6 months
- at 12 months
- annually thereafter.

Leukoplakia

Leukoplakias are clinical white patches that cannot be wiped off the mucosa and cannot be classified clinically or microscopically as another specific disease entity (such as lichen planus). Leukoplakia is thus a clinical diagnosis only and can only be made by exclusion. Leukoplakia can be totally benign or sometimes can be precancerous or a marker for cancer elsewhere in the upper aerodigestive tract.

Incidence

Occurs in about 0.1% of the population.

Age

Occurs predominantly in the middle-aged and elderly.

Sex

Occurs more in men than women.

Geographic

It has no known geographic incidence.

Predisposing factors

These are habits such as:

- tobacco use
- betel use
- alcohol use
- use of sanguinarine.

Clinical features

Leukoplakias vary in size: some are small and focal, others more wide-spread – occasionally involving very large areas of the oral mucosa – and in other patients several discrete separate areas of leukoplakia can be seen. Leukoplakia has a wide range of clinical presentations, from homogeneous

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wide range of grades of dysplasia in different parts of a lesion and carcinoma in up to 50%.

Features of biopsy

Leukoplakias show, to a varying degree, three main microscopic features.

- **Increased keratin production:** increased keratin produces the white clinical appearance of keratoses. If nuclei persist into the superficial cell layers the term 'hyperparakeratosis' is used, whereas if there is excessive mature keratin, with a prominent granular cell layer, the term 'hyperorthokeratosis' is applied. Any leukoplakia can show either or both types of change, neither of which are an index of premalignancy.
- **Change in epithelial thickness:** thinning (hypoplasia) or thickening (hyperplasia) may be present and, although neither are indices of premalignancy, malignant change is more likely in a hypoplastic epithelium.
- **Disordered epithelial maturation:** although clinical features, such as the admixture of red lesions, may suggest the degree of premalignant potential of a keratotic lesion, histological assessment of the degree of disordered proliferation, maturation and organisation of the epithelium (i.e. the degree of dysplasia) continues to provide the best guide. It is accepted that dysplasia may precede malignant change – the connotation of severe dysplasia being that malignant change is likely. However, some lesions that often do become malignant (such as some sublingual keratoses) do not always show a great deal of dysplasia. It is clear that only a minority of leukoplakias are preneoplastic, but the problem is to identify those which are.

Oral brush biopsy

Computer-assisted analysis of an oral brush biopsy is an aid to the oral examination which helps determine the significance of oral lesions with an epithelial abnormality. It is especially valuable for benign-appearing lesions that are easily overlooked and unrecognised, but in fact are malignant or potentially malignant. In a US multicentre clinical trial of nearly 1000 patients conducted at 35 academic dental centres, this technique proved to independently detect all histologically confirmed premalignant and cancerous lesions. Furthermore, dysplasia or carcinoma were uncovered in 4.5% of benign-appearing lesions clinically judged harmless.

The brush biopsy is performed without any anaesthetic and using an instrument designed to obtain a transepithelial specimen containing cells from the basal, intermediate and superficial layers. This is a crucial feature, since the basal cell layer may be the only layer of the epithelium that contains abnormal cells within a potentially malignant or malignant lesion.

The laboratory evaluates every specimen for adequacy by verifying cellular representation from each layer of the epithelium, so false-negative results due to inadequate technique are minimised. The cellular morphology of the cells obtained by the brush biopsy is used to classify each brush biopsy specimen. A 'negative' result indicates that no epithelial abnormality was detected. Brush biopsy specimens displaying images of abnormal cells are classified as either 'positive' or 'atypical'. A histological section is always required to 'grade' any abnormality uncovered.

Identifying malignant change

Not all dysplastic lesions are premalignant, though many are. Dysplasia may also be seen in regenerating tissue and in some infections. Histopathology alone clearly cannot always identify early malignant changes, since it samples only a small area and, furthermore, is subjective and there can be both inter- and intra-examiner variability. Conversely, while the potentially malignant nature of leukoplakias is stressed, several studies have shown that dysplastic lesions can sometimes regress spontaneously, with rates ranging from 9% to 45%. It is not at present possible reliably to predict which dysplastic lesions will progress to carcinoma and which will regress. Over the last few years, much effort has gone into identifying the genetic changes that underlie oral carcinoma and biomarkers such as DNA ploidy, p53 mutations, and chromosome 3 and 9 changes appear to predict neoplastic change. Overall,

- around 2–5% of leukoplakias become malignant in 10 years
- 5–20% of leukoplakias are dysplastic
- of leukoplakias with dysplasia, 10–35% proceed to carcinoma.

Management

Some patients have spontaneous remission of leukoplakia, but the lesion may be potentially malignant and thus both behaviour (lifestyle) modification and active treatment of the lesion are indicated. The prevalence of malignant transformation in leukoplakias is 2–35% over 10 years and is highest in lesions with severe dysplasia. Patient information is an important aspect in management.

- Removal of known risk factors (tobacco, alcohol and trauma) is a mandatory first step. Success is difficult to achieve: in one series of 145 patients operated on for oral leukoplakias, only 20 gave up smoking and only five stopped drinking alcohol.
- The patient should be re-examined 3 months after instituting this. If the lesion persists, it should be removed. However, many patients with leukoplakias belong to lower socio-economic groups and do not always

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and minimal inflammation, some 5% of such patients subsequently developed oral squamous cell carcinoma.

- Resection with a scalpel or laser is probably the most effective and safe means of removing pathologic tissue since – unlike the case with cryosurgery, coagulation or laser vaporisation – a specimen for pathologic evaluation (of histology and margins) is produced, and the pain and postoperative scarring are less with these techniques than with coagulation. Finally, laser excision (usually with the carbon dioxide laser) seems to have advantage over the use of a scalpel, as intraoperative bleeding and the need for mucosal or dermoepidermal flaps are reduced.
- Follow-up; patients should be regularly checked at 3, 6, and 12 months, and then annually for any:
 - size change
 - appearance of red lesions
 - ulceration
 - recurrences
 - new lesions.

Medical therapies

- Up to 30% of leukoplakias can markedly improve or even resolve when aetiological factors are removed and medical therapies (anti-inflammatory and antimycotic therapy) used. Up to 60% of leukoplakias regress or totally disappear if tobacco use is stopped. Leukoplakias induced by smokeless tobacco may resolve if the habit is stopped. Some candidal leukoplakias respond at least partially to antifungal drugs (smoking should also be stopped) and dysplasia may regress.
- Topical anticancer drugs or retinoids can cause regression and are generally well tolerated and effective, but their efficacy is only temporary, and perhaps their best indication is when the location or extent of the lesion render surgical removal difficult. Topical treatment of leukoplakia with podophyllin solution or bleomycin has induced some regression or even total resolution of dysplasia and clinical lesions, and lesions recur more slowly than after surgery. Treatment with photodynamic therapy, in which a light-sensitising dye is given to the patients, and light shone on the lesion to activate the dye and cause necrosis of the pathological tissue, is still in its infancy.
- Since leukoplakias are only potentially cancerous, it is generally accepted that radiotherapy or systemic chemotherapy are inappropriate treatments.

Chemoprevention

Two different approaches have been proposed for clinical chemoprevention trials:

- **Chemoprevention by treatment of oral leukoplakias to prevent malignant transformation.** 13-cis-Retinoic acid can result in lesions regressing, but side-effects are severe and many patients do not complete the planned treatment. Moreover, lesions recur a few months after the end of the intervention. However, it is now possible to treat 'condemned at risk mucosa', though reversal of leukoplakia has not been proved to reduce the risk of developing cancer.
- **Chemoprevention in patients following removal of leukoplakias.** Fenretinide used in patients with negative histology for cancer following laser excision of leukoplakias is well tolerated and the preliminary results show a significant protective effect. Unfortunately, the drug is not readily available.

In summary, chemoprevention with retinoids is not a definitive treatment because:

- after the treatment has stopped, lesions recur in a large number of cases
- adverse effects are common
- most are teratogenic.

Summary

No clinical or histological characteristics are able to reliably predict potential malignancy in leukoplakias; neither have reliable biological markers of

Table 25.4 Minimal treatment for leukoplakia			
Location	No dysplasia	Mild dysplasia	Moderate or severe dysplasia
Buccal	Watchful waiting	Watchful waiting or remove	Remove
Hard palate	Watchful waiting	Watchful waiting or remove	Remove
Dorsum of tongue	Watchful waiting	Watchful waiting or remove	Remove
Ventrum of tongue/ floor of mouth	Watchful waiting	Remove	Remove
Lateral border of tongue	Watchful waiting	Remove	Remove
Fauces	Watchful waiting	Remove	Remove
Vermilion	Watchful waiting	Remove	Remove

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Reverse smoking (bidi)

PDFFREE.COM In some communities, especially in Asia, cigarettes are smoked with the lit end within the mouth. Palatal or other oral carcinoma can result.

Pipe smoking

Diffuse whiteness over the palate is termed 'smoker's keratosis' or 'stomatitis nicotina'. The palatal minor salivary gland orifices appear red against this white background. Malignant change is uncommon.

Cigar smoking

Cigar smokers may develop stomatitis nicotina and nicotine-stained teeth. Malignant change is uncommon.

Detection of cancer and potentially malignant lesions

Unfortunately, many of the population – especially those at highest risk, such as elderly men who smoke and drink – do not seek regular dental care. Patients often present late to physicians and with advanced tumours, and treatment is then usually more mutilating, with higher morbidity and costs, and a worse prognosis. Furthermore, physicians and surgeons have often received little or no training in the examination of the mouth.

Clinicians should be aware that single ulcers, lumps, red patches or white patches – particularly if any of these are persisting for more than 3 weeks, may also be manifestations of frank malignancy: biopsy is invariably indicated. Even common, benign-looking oral lesions attributed to friction or trauma require evaluation when they persist. It should be noted that clinically differentiating potentially malignant and malignant oral lesions from those that are benign, even by highly trained professionals, is a difficult task. This is because these lesions do not often display well-defined clinical features that facilitate their recognition. Not uncommonly, potentially malignant and malignant oral lesions are asymptomatic, appear innocuous and are easily overlooked. Yet fewer than 25% of all leukoplakias, the most common potentially malignant lesions, are ever subjected to biopsy. As a result, many are left to progress to more advanced stages or cancer.

Tobacco-induced keratoses

Tobacco is a common cause of keratosis. Men especially are affected. Tobacco use is one of the major risk factors for oral carcinoma and, if smoked, also predisposes to cancers elsewhere in the upper aerodigestive tract, bladder and other sites. Tobacco use should thus be discouraged; nicotine patches or the drug Zyban (bupropion) may help users break the habit.

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Diagnosis

The diagnosis is clinical and, apart from removing irritants and ceasing habits, no active treatment is required.

Management

Patient information is an important aspect in management. Frictional keratosis is completely benign, and does not require treatment. There is no evidence that continued minor trauma alone has any carcinogenic potential but, if the patient is causing the lesion from some habit, that should be stopped.

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Figure 26.1 Fordyce spots

Clinical features

Fordyce spots are yellowish soft granules beneath the oral mucosa caused by ectopic sebaceous glands. They are extremely common and are usually seen in the buccal mucosa particularly inside the commissures, and also in the retromolar regions and lips. They may be seen as creamy yellow dots along the border between the vermilion and the oral mucosa of the upper lip (Fig. 26.1).

Fordyce spots are extremely common: probably 80% of the population have them, but they are not usually evident in infants (though they are present histologically), appearing in children after the age of 3 years, increasing during puberty and then again in later adult life.

They are totally benign, though the occasional patient becomes concerned about them or they are mistaken for thrush or lichen planus.

Diagnosis and management

The spots are totally benign, though the occasional patient or physician becomes concerned about them or misdiagnoses them as, for example, thrush or lichen planus. No treatment is indicated, other than reassurance.

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existing papillae. Older lesions may become red if inflamed. There is a positive correlation between the severity of overgrowth and gingival inflammation, plaque score, calculus accumulation and pocket depths. There is no correlation between the extent of overgrowth and the dose of phenytoin, its serum level, or the age and sex of the patient. Histology shows marked thickening of epithelium with long overgrowths into the connective tissue. Fibroblasts show increased mitotic activity, but are not increased in number, and the collagen fibre component is not increased.

- Ciclosporin (cyclosporin) is an immunosuppressive drug particularly used to suppress the cell-mediated response after organ transplants, and can cause gingival swelling initially affecting the gingival papillae, but only a third of patients may be affected, more commonly children.
- Calcium-channel blockers, which are mainly used as anti-hypertensive agents (especially nifedipine), cause, in some individuals, gingival hyperplasia typically affecting the papillae which become red and puffy and tend to bleed. Increased numbers of fibroblasts containing strongly sulphated mucopolysaccharides may be demonstrated histochemically; their cytoplasm contains numerous secretory granules, suggesting an increased production of acid mucopolysaccharides.

Diagnosis

This is usually a clinical diagnosis. Blood picture or biopsy are rarely indicated.

Management

Treatment of drug-induced hyperplasia poses some problems. The physician may be willing to substitute another drug but, in any event, the patient's level of plaque control often needs considerable improvement and a chlorhexidine mouthwash may be helpful. Excision of enlarged tissue may be indicated, but difficult if the tissue is very firm and fibrous. Healing may be slow, possibly hampered by infection of the large wound. Unfortunately, the gingival enlargement readily recurs, although this is less likely with meticulous oral hygiene, particularly if the drug has been stopped. Therefore:

- treat predisposing factors
- improve oral hygiene
- gingivoplasty where indicated.

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- Sarcoidosis.
- Crohn's disease. Regional ileitis may follow some years later.
- Orofacial granulomatosis – from an adverse reaction to various food additives. These additives include cinnamic aldehyde, butylated hydroxytoluene or dodecyl gallate (in margarine), or menthol (in peppermint oil), though these reactions are by no means always relevant; for example, only one out of nine patients in one study had a relationship with such additives.

Clinical features

The onset is usually in young adult life and has no racial predilection. The earliest manifestation is sudden diffuse or occasionally nodular swellings of the lip involving, in decreasing order of frequency, the upper lip and the lower lip and one or both cheeks. Less commonly, other areas, the forehead, the eyelids or one side of the scalp may be involved as well or in isolation. Cheilitis granulomatosa is episodic with non-tender swelling and enlargement of one or both lips (Fig. 28.1). The lip involved may feel soft, firm or nodular on palpation. The normal lip architecture is eventually altered by the presence of lymphoedema and non-caseating granulomas in the lamina propria. Lingual, palatal, gingival and buccal involvement also may occur. At the first episode the oedema typically subsides completely in hours or days, but after recurrent attacks the swelling may persist, and slowly increases in degree. The swelling eventually becomes permanent. Recurrences can range from days to years; however, once chronicity is established, the enlarged lip appears cracked and fissured, with reddish brown discoloration and scaling. The fissured lip becomes painful. It eventually acquires the consistency of firm rubber. After some years, the



Figure 28.1 Granulomatous cheilitis

swelling may very slowly regress. There may be splitting of the lips and angular stomatitis.

Ulcers classically involve the buccal sulcus where they appear as linear ulcers, often with granulomatous masses flanking them. Mucosal lesions also include thickening and folding of the mucosa to produce a 'cobblestone' type of appearance and mucosal tags. Purple granulomatous enlargements may appear on the gingiva.

The attacks are sometimes accompanied by fever and mild constitutional symptoms, including headache and even visual disturbance. The regional lymph nodes are enlarged in 50% of cases, but not usually very greatly.

A fissured or plicated tongue is seen in 20–40% of cases. It is present from birth in some, which may indicate genetic susceptibility. There may be loss of sense of taste and decreased salivary gland secretion.

Facial palsy of the lower motor-neurone type occurs in some 30% of cases. It may precede the attacks of oedema by months or years, but more commonly develops later. Though intermittent at first, the palsy may become permanent. It may be unilateral or bilateral, and partial or complete. Other cranial nerves (the olfactory, auditory, glossopharyngeal and hypoglossal) may occasionally be affected. Involvement of the central nervous system has also been reported, but the significance of the resulting symptoms is easily overlooked as they are very variable, sometimes simulating multiple sclerosis but often with a poorly defined association of psychotic and neurological features. Autonomic disturbances may occur.

Diagnosis

The many causes of oedema of the lips make the diagnosis one based on exclusion, on clinical signs and on histological examination. The essential feature is the chronic non-tender swelling of the lip. In the early attacks clinical differentiation from angioedema may be impossible in the absence of either plicated tongue or facial palsy, but persistence of the swelling between attacks should suggest the diagnosis.

In the established cases, other causes of macrocheilia must be excluded. Ascher syndrome associated with blepharochalasia is likely to cause confusion, although the swelling of the lip is caused by redundant salivary tissue and is present from childhood (see Ch. 37). Lymphoma is a rare differential diagnosis. Biopsy of the swollen lip or facial tissues is indicated, but during the early stages often shows only lymphoedema and perivascular lymphocytic infiltration. However, although the histological changes are not always conspicuous or specific in many cases of long duration, the infiltrate becomes more dense and pleomorphic and small focal granulomas are formed, indistinguishable from Crohn's disease or sarcoidosis.

Investigation of the gastrointestinal tract (endoscopy, radiography and biopsy) is mandatory to exclude Crohn's disease. Investigations such as chest radiography, serum angiotensin converting enzyme, and a gallium scan may be required to exclude sarcoidosis. Patch tests may be indicated to exclude reactions to various foodstuffs or additives.

Management

Reactions to dietary components should be sought and possible provoking substances avoided. Elimination diets may be warranted in some patients.

Conservative management includes intralesional corticosteroid injections, non-steroidal anti-inflammatory agents, antibiotics, antimalarials, and mast cell stabilisers. Clofazimine appears to help the majority of patients.

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Herpesvirus Infections

Introduction

Herpesviruses are DNA viruses that are mostly:

- contracted in early life
- transmitted in saliva
- characterised by latency
- reactivated during immunosuppression
- cause more severe and protracted disorders in patients with compromised immunity, particularly in HIV infection, in cancer patients and in those immunosuppressed after organ grafts.

They include herpesviruses:

- herpes simplex type 1 (HSV-1)
- herpes simplex type 2 (HSV-2)
- herpes varicella-zoster (VZV)
- Epstein-Barr virus (EBV)
- cytomegalovirus (CMV)
- human herpesvirus type 6 (HHV-6)
- human herpesvirus type 7 (HHV-7)
- human herpesvirus type 8 (HHV-8).

Herpesviruses can sometimes cause malignant tumours (i.e. are *oncogenic*).

Herpes simplex virus

The term 'herpes' is often used loosely to refer to infections with herpes simplex virus (HSV), a ubiquitous virus which commonly produces lesions

in the mouth and oropharynx. Primary infection is often subclinical between the ages of 2-4 years and is a common cause of 'teething'. Herpetic stomatitis (gingivostomatitis) is:

- the primary clinical infection with HSV
- usually caused by HSV-1
- seen mainly between the ages of 2 and 4 years
- increasingly seen in older patients
- especially seen in teenagers, sometimes due to HSV-2 transmitted sexually and may mainly cause oropharyngeal soreness
- generally speaking, is caused above the belt (oral or oropharyngeal) by HSV-1, but caused below the belt (genital or anal) by HSV-2.

Incidence

Common, especially in lower socio-economic conditions.

Age

Primary stomatitis is seen mainly in children and adolescents. Oropharyngeal herpes is seen mainly in adolescents and recurrences are seen mainly in adults.

Sex

Both sexes are affected.

Geographic

Common in children in the developing world. Also seen in adults, especially in the developed world.

Predisposing factors

- Herpes simplex virus is contracted from infected saliva or other body fluids after an incubation period of approximately 4-7 days.
- Close contact with infected individuals, such as in play groups or sexually, predisposes to infection.
- HSV-1 can cause oral or oropharyngeal infection, usually via infection from saliva, and is most frequent and at a lower age in lower socio-economic groups
- HSV-2 can cause severe oropharyngeal infection, usually via orogenital or oro-anal sexual contact.

Herpes simplex virus anogenital infection is contracted from infected semen, saliva or other body fluids. It is more common in the sexually active and is most frequent amongst female prostitutes (75%) and men who have sex with men (80%). HSV-1 genital infection is usually less common and less severe than HSV-2 infection.

- Patients with immune defects are liable to severe and/or protracted HSV infections.

Aetiology and pathogenesis

- HSV must contact mucosae or abraded skin to initiate infection.
- HSV surface glycoproteins mediate cell attachment and penetration.
- Primary infection is when a susceptible (non-immune) individual develops infection.
- Initial infection occurs when an individual who has antibodies to either HSV-1 or HSV-2 is infected with the other virus type for the first time.
- HSV is neuroinvasive and neurotoxic and infects neurones of dorsal root and autonomic ganglia.
- HSV remains latent thereafter in the ganglion, usually the trigeminal ganglion, but can be reactivated to result in clinical recrudescence (see below).
- HSV is also implicated in Bell's palsy (see Ch. 18) and erythema multiforme (see Ch. 24).

Clinical features

Some 50% of primary HSV infections are subclinical. The main features of clinical primary disease are that:

- The mouth or oropharynx is sore (herpetic stomatitis). Other features include:
 - A single episode of oral vesicles which may be widespread, and break down to leave oral ulcers. These are initially pin-point, but fuse to produce irregular painful ulcers (Fig. 29.1).



Figure 29.1 Herpetic stomatitis; ulcers in the palate

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Table 29.1 Antiviral therapy of oral herpes simplex infections in the otherwise apparently healthy patient

Infection	Therapy
Herpes simplex stomatitis	Aciclovir 100–200 mg tablets 5 times daily, or oral suspension (200 mg/5 ml) 5 times daily
Recurrent herpes labialis	Penciclovir 1% cream every 2 hours or 5% aciclovir cream every 2 hours

Recurrent herpetic infections

Incidence

Up to 15% of the population have recurrent HSV-1 infections.

Age

They occur mainly in adults.

Sex

Both sexes are affected.

Geographic

Herpes labialis is most common in sunny climes.

Predisposing factors

Reactivating factors include:

- fever, such as caused by upper respiratory tract infection (hence herpes labialis is often termed ‘cold’ sores)
- sunlight
- trauma
- immunosuppression.

Aetiology and pathogenesis

HSV-1 is latent in the trigeminal ganglion after primary infection. The virus can be reactivated, is shed into saliva, and there may be clinical recrudescence, recurrently, to produce herpes labialis or, occasionally, intraoral ulceration.

Clinical features

- Features of recurrent herpes labialis are:
 - lip lesions at the mucocutaneous junction (Fig. 29.2)
 - lesions may be preceded by pain, burning, tingling or itching

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- Lip lesions in healthy patients may be minimised with penciclovir 1% cream or aciclovir 5% cream applied in the prodrome.
- Lip lesions in immunocompromised patients may require systemic aciclovir or other antivirals such as valciclovir (the precursor of penciclovir).
- Recurrent intraoral herpes in healthy patients can be managed with symptomatic treatment with a soft diet and adequate fluid intake, antipyretics/analgesics (paracetamol elixir), and local antiseptics (0.2% aqueous chlorhexidine mouthwashes). Systemic aciclovir or other antivirals such as valciclovir may be indicated for persistent lesions.
- Recurrent intraoral herpes in immunocompromised patients is difficult to manage and systemic aciclovir or other antivirals may well be needed. A soft diet and adequate fluid intake, antipyretics/analgesics (paracetamol elixir) and local antiseptics (0.2% aqueous chlorhexidine mouthwashes) may help.
- Antiviral resistance is becoming a significant problem to immunocompromised persons, especially those with a severe immune defect.

Herpes varicella-zoster virus infections

Chickenpox (varicella)

This is the primary infection with the virus.

Incidence

It is common.

Age

It mainly occurs in children.

Sex

Both sexes are affected.

Geographic

No known geographic incidence, it occurs worldwide.

Predisposing factors

Chickenpox is highly contagious and is spread by droplets.

Aetiology

After this primary infection, the virus remains latent in dorsal root ganglia.

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Predisposing factors

Zoster mainly affects the elderly, or immunocompromised, such as in HIV infection, leukaemia or cancer. Zoster has become a fairly common feature in HIV-infected patients treated with HAART (see Appendix 2 and Ch. 38).

Aetiology

Reactivation of VZV latent in sensory ganglia.

Clinical features

- The main features are pain and a rash in one dermatome – the area of skin and mucosa supplied by a sensory nerve.
- Most zoster is seen in the thoracic region; 30% is in the trigeminal region.
- Pain occurs before, with and after the rash.
- Rash is unilateral vesiculating then scabbing in dermatome (Fig. 29.4).
- Mouth ulcers are seen in maxillary or mandibular zoster only:
 - mandibular zoster – ipsilateral on buccal and lingual mucosa

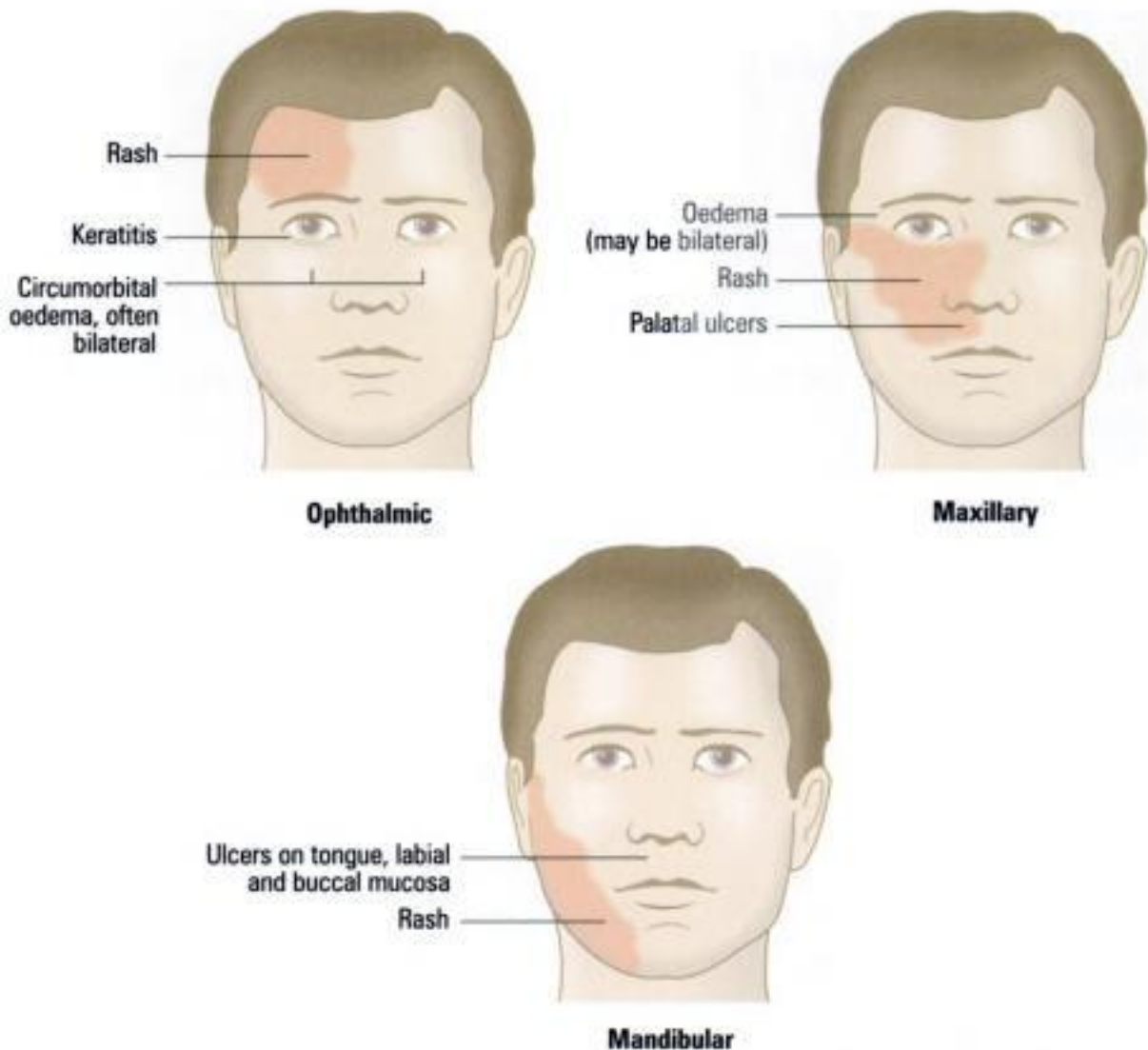


Figure 29.4 Zoster can affect any of the three divisions of the trigeminal nerve

- maxillary – ipsilateral on palate and vestibule.

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- **Postherpetic neuralgia** (see Ch. 36) is the condition when the pain persists long after the rash has healed.

Diagnosis

Diagnosis is clinical; differentiation from toothache and other causes of ulcers, especially HSV, is important.

Management

- Management is with analgesics.
- Aciclovir (high dose) orally or parenterally may help pain and healing and prevent postherpetic neuralgia.
- Systemic corticosteroids may have a similar effect.
- In ophthalmic zoster an ophthalmological opinion is important, since there can be corneal ulceration.

Epstein–Barr virus infection

EBV is a ubiquitous virus that commonly produces lesions in the mouth and oropharynx.

Incidence

It is common, especially in lower socio-economic conditions.

Age

Infection is common among young adults (especially students) and is often subclinical.

Sex

Both sexes are affected.

Geographic

Common in the developing world. Also seen in adolescents and adults in the developed world.

Predisposing factors

- EBV is contracted from infected saliva or other body fluids after an incubation period of approximately 20–40 days.
- EBV is found in pharyngeal epithelium and appears in the saliva from patients with infectious mononucleosis and for several months after apparent recovery.
- Close contact with infected individuals, such as sexually, predisposes

to infection, which appears to be spread by close oral contact such as kissing.

- Patients with immune defects are liable to severe and/or protracted infections or the virus may be reactivated leading to recurrence of infectious mononucleosis or, rarely, producing lymphoproliferative disease.

Clinical features

The clinical features are as follows:

- EBV can cause a glandular fever syndrome termed 'infectious mononucleosis'.
- Infectious mononucleosis is protean in its clinical manifestations which include mainly:
 - lymphadenopathy
 - sore throat
 - fever
 - malaise
 - rashes.

Particular features predominate in some patients.

- In the anginose type of infectious mononucleosis (sore-throat type), the throat is sore with soft palate petechiae and a whitish exudate on oedematous tonsils. Pharyngeal oedema may threaten the airway.
- The glandular type of infectious mononucleosis is characterised mainly by general lymph node enlargement and splenomegaly.
- The febrile type of infectious mononucleosis is characterised mainly by fever.

Recovery can take weeks or months and the virus thereafter remains latent in pharyngeal and/or salivary epithelial cells.

Complications

EBV is also implicated in:

- rashes of a non-allergic nature affecting the extensor surfaces of the limbs in patients taking ampicillin or amoxicillin with infectious mononucleosis
- hairy leukoplakia
- chronic infection which may cause persist malaise
- Burkitt's lymphoma
- post-transplantation lymphoproliferative disorder
- nasopharyngeal carcinoma (see Ch. 20).

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• glandular-fever-type syndromes (Table 29.2)

• facial palsy.

- HHV-7 is not of any known relevance to oral health.
- HHV-8 is a recently discovered DNA virus transmitted mainly sexually and strongly associated with Kaposi sarcoma.

Websites

<http://www.entnet.org/cankerfever.html>

<http://www.herpess.com/overview.shtml>

<http://www.herpess.com/references.shtml>

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Lichen Planus

Introduction

Lichen planus (LP) is an inflammatory autoimmune-type of mucocutaneous disease which can affect stratified squamous epithelium of the skin, oral mucosa and genitalia.

Incidence

Lichen planus is not uncommon and has a prevalence of the order of 1%.

Age

It usually affects persons between the ages of 30 to 65 years.

Sex

There is a slight female predisposition to LP.

Geographic

LP is seen worldwide.

Predisposing factors

- There is no definitive immunogenetic basis yet established for LP, but studies have reported various HLA associations:
 - in cutaneous LP: an increase in HLA-DR1 (mainly HLA-DRB1*0101), DQ1, DR3 or DR9

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propria (mainly T CD8⁺ cells), suggesting a cell-mediated immune response.

- Apoptosis (controlled cell death) is then seen in the basal epithelium, probably caused by the profound T-cell infiltrate and production of tumour necrosis factor- α (TNF- α) and interferon- γ (IFN- γ)
- Although immune deposits are seen, typically fibrin and sometimes IgM at the basement membrane zone and in colloid bodies, they probably represent non-specific exudation and not autoantibodies. They can be diagnostically helpful.

Clinical features

- Six clinical types of oral LP have been reported:
 - reticular, a network of raised white lines or striae (reticular pattern)
 - papular, white papules (Fig. 30.1)
 - plaque-like, simulating leukoplakia (Fig. 30.2)
 - red atrophic areas – LP is one of the most common causes of desquamative gingivitis.
 - erosive/ulcerative erosions that are persistent, irregular, and painful, with a yellowish slough (this type is less common)
 - bullous.
- LP is often asymptomatic, but there may be soreness from atrophic areas of thin, red mucosa or erosions. White lesions are usually asymptomatic, however; mild oral discomfort or burning sensations are the most common complaints in symptomatic cases.
- LP typically results in lesions which are:
 - mostly white



Figure 30.1 Papuloreticular lichen planus



Figure 30.2 Lichen planus of the plaque type, resembling leukoplakia

- most often reticular, but may be papular or plaque-like and associated with red atrophic areas
- in the posterior buccal mucosa bilaterally
- on the dorsum of the tongue
- on the lips
- rarely, on the palate.
- Occasionally the gingiva may be affected with a white lacework of fine white lines and papules. A 'desquamative gingivitis' may also develop in about 25% of patients with erosive LP and can be the initial or the only sign of oral involvement.

Prognosis

Often the onset of lichen planus is slow, taking months to reach its peak. It often clears from the skin within 18 months, but in a few people persists for many years. Oral lesions are often persistent.

Malignant potential

Lichen planus has a small premalignant potential – probably of the order of <1%, and predominantly in non-reticular LP (Fig.30.3).

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Figure 30.4 Lichenoid lesions related to an amalgam restoration

- diabetes mellitus
- graft-versus-host disease
- hepatic disease or hepatitis virus infection.

Lichenoid lesions resemble LP, but may:

- be unilateral
- be associated with erosions
- resolve on discontinuation of the offending drug.

Lichenoid lesions are more likely than LP to be associated with:

- a mixed cellular infiltrate including plasma cells and eosinophils
- a deeper infiltrate
- a perivascular infiltrate
- parakeratosis
- colloid bodies in the epithelium
- basal cell autoantibodies.

Skin testing for hypersensitivity to drugs or dental materials is only rarely of clinical value.

Lichen planus is often fairly obviously diagnosed from the clinical features, but it can closely simulate other conditions such as:

- lupus erythematosus
- chronic ulcerative stomatitis
- keratosis
- carcinoma.

The firm diagnosis of LP therefore relies upon biopsy and histopathological examination of lesional tissue, occasionally aided by direct immunostaining. Often the histological and immunological findings revealed are no more than 'consistent with lichen planus', but at least serve to exclude

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Management

Treatment is not always necessary, unless there are symptoms. Patient information is an important aspect in management. Unfortunately, although the natural history of cutaneous LP is one often of remission, oral LP remits only in a few patients, and thus treatment is indicated for symptomatic LP (Fig. 30.5).

Predisposing factors should be corrected:

- It may be wise to consider removal of dental amalgams if the lesions are closely related to these, or unilateral, but there are no tests such as patch tests that will reliably indicate which patients will benefit from this.
- If drugs are implicated, the physician should be consulted as to possible changes in therapy.
- If there is HCV infection, this should be treated by a physician.
- Improvement in oral hygiene may result in some subjective benefit. Thus good oral hygiene should be maintained. Chlorhexidine or triclosan mouthwashes may help.
- Symptoms can often be controlled with topical medication such as topical corticosteroids and topical tacrolimus.

Severity-dependent treatment

Mild LP

Topical corticosteroids are the mainstay of therapy, although erosive and gingival lesions are often recalcitrant. High potency corticosteroids such as clobetasol, fluocinonide or fluticasone may initially be employed and should then be changed to a lower potency drug (e.g. hydrocortisone hemisuccinate, triamcinolone acetate or fluocinolone). Topical creams or pastes can be applied in a suitable customised tray or veneer to be worn at night.

Moderate LP

If there is severe or extensive oral involvement, topical ciclosporin or tacrolimus may be of significant benefit, often being used along with a high or super potent topical steroid. This regimen is useful in the management of LP-related desquamative gingivitis recalcitrant to other therapies.

Severe LP

In severe LP in multiple sites, patients may require systemic corticosteroids, azathioprine, cyclophosphamide, hydroxychloroquine, acitretin, thalidomide or ciclosporin. Dapsone is occasionally effective.

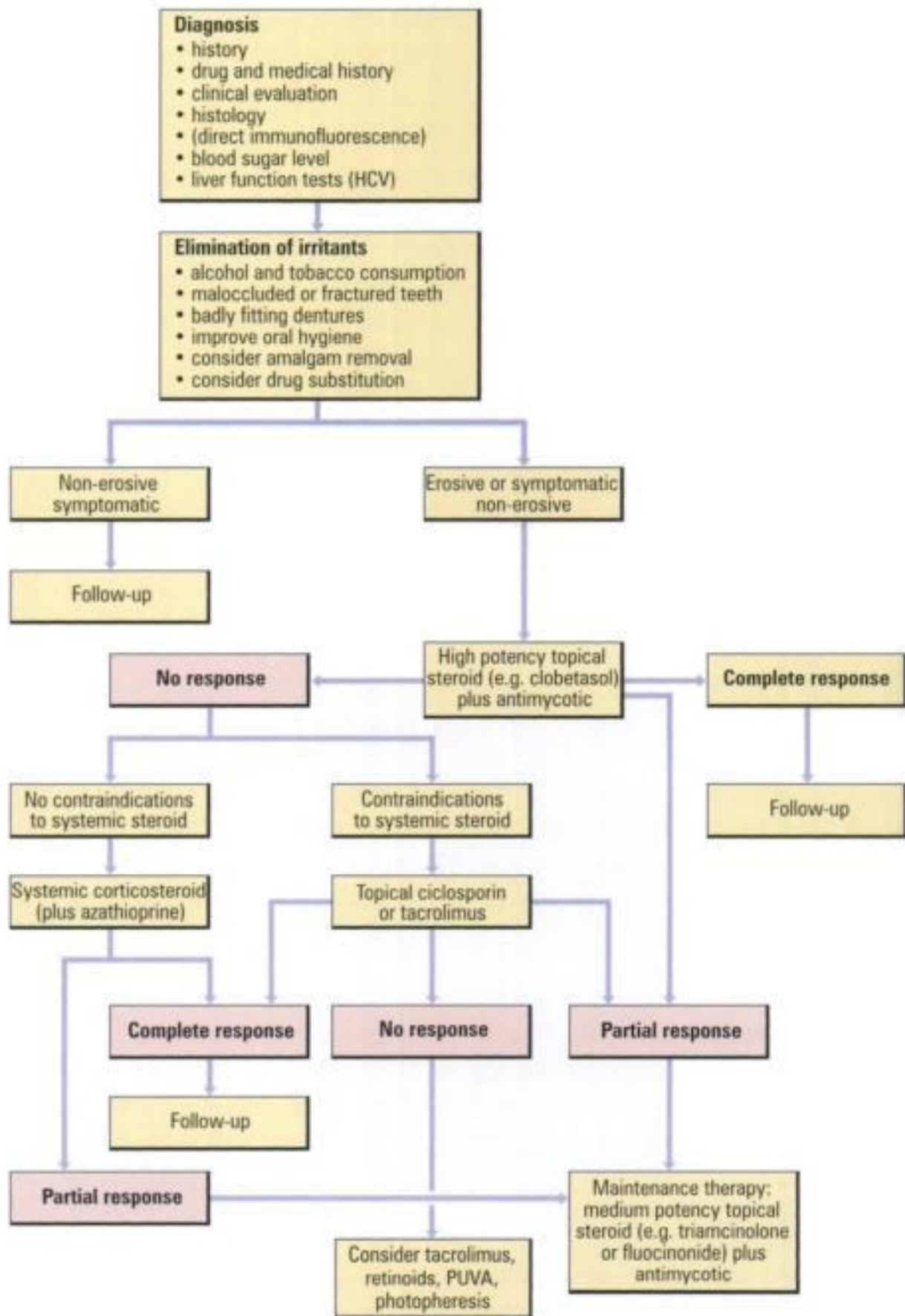


Figure 30.5 Algorithm for the management of lichen planus

Failure to respond to treatment

If LP fails to respond to topical measures, systemic immunomodulators may be required, under specialist supervision. These include:

- Systemic corticosteroids, e.g. prednisolone (see Appendix 2).
- Other immunomodulatory agents (e.g. azathioprine, ciclosporin, interferon).
- Thalidomide may be effective against severe LP. However, it is rarely indicated since it is teratogenic and can produce neuropathies.
- Other therapies for LP include retinoids, dapsone, low molecular weight heparin and many others, but either their efficacy has not been well proven or they have unacceptable adverse effects.

Antifungals may help, especially where there is candidal superinfection. Patients with non-reticular lichen planus should be monitored to exclude development of carcinoma. Tobacco and alcohol use should be minimised.

Websites

<http://www.aarda.org/indexf.html>

The International Oral Lichen Planus Support Group: <http://www.tamcd.edu/lichen>

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Odontogenic Cysts and Tumours

Odontogenic cysts

A cyst is a pathological cavity having liquid, semi-liquid or gaseous contents. It is frequently, but not always, lined with epithelium.

Cysts of the jaws mostly arise from odontogenic epithelium, and are relatively common lesions. Inflammatory cysts are the most frequent, accounting for about 55% of all jaw cysts.

Aetiology and pathogenesis

The main aetiopathogenic factors for cysts are:

- Epithelial proliferation, either stimulated by inflammation in the case of radicular cysts, or occurring without apparent stimulation in the case of keratocysts.
- Hydrostatic or osmotic factors, which may play a part in cyst growth since the cyst wall acts as a semipermeable membrane.
- Keratin formation, which may be prominent in keratocysts.
- Bone resorbing factors, such as prostaglandins, which have been demonstrated in tissue cultures from cysts, and collagenase may be present in the walls of keratocysts.

Clinical features

Odontogenic cysts are generally slow growing and expansive and are often found as symptomless coincidental radiographic findings. They may reach a large size before they give rise to symptoms, such as:

- Noticeable swelling; cysts in bone initially produce a smooth bony hard lump with normal overlying mucosa but, as the bone thins, it may crackle on palpation rather like an egg shell (termed 'egg shell crack-

ing'). When the overlying bone is resorbed, the cyst may show through as a bluish fluctuant swelling (Fig. 31.1).

- Discharge into the mouth.
- Pain due to secondary infection.

Diagnosis

The diagnosis is based on the combination of an adequate history, clinical examination, and selected investigations. Appropriate tests include pulp vitality testing of associated teeth, radiographs (both intraoral and extraoral), aspiration and analysis of cyst fluids, and histopathology.

Management

Cysts are managed either by enucleation or by marsupialisation. Enucleation is the complete removal of the cyst, and has the advantages of leaving behind no pathological tissue and of permitting histopathological examination of the complete cyst. In marsupialisation, only part of the cyst can be histologically examined; some pathological tissue is left *in situ*; and healing is slower.

Inflammatory cysts

By far the most common of all jaw cysts are inflammatory cysts arising in association with a non-vital tooth. These include:

- Radicular cyst (dental cyst), where the cyst is associated with the apex of a non-vital tooth.
- Lateral periodontal cyst, where the cyst is found to lie on the lateral aspect of a non-vital tooth, usually associated with a lateral pulp canal



Figure 31.1 Odontogenic cyst

and foramen. From time to time periodontal cysts may be found in association with a vital tooth, due to periodontal inflammation or periodontitis (particularly with a mandibular third molar tooth).

- Residual cysts, where one of the above inflammatory cysts (usually a radicular cyst) remains after removal of the non-vital tooth from which it arose.

The epithelial lining is derived from the epithelial rests of Malassez which proliferate to produce thick irregular squamous epithelium. The epithelium is often incomplete, with granulation tissue forming the cyst wall in the denuded areas. Depending on the nature of the inflammatory response there may be areas of chronic inflammation, or acute inflammation with abscess formation. Cholesterol crystal clefts are often present and mucous cells may be found. The cyst capsule consists of collagenous fibrous connective tissue. The cyst fluid is usually watery but may be thick and viscid with cholesterol crystal clefts giving it a shimmering appearance. These cysts cause resorption of bone and may erode the cortical plates and become quite large.

Diagnosis

The diagnosis is based on the combination of an adequate history, clinical examination and selected investigations. Appropriate tests include pulp vitality testing of associated teeth, radiographs (both intraoral and extraoral), aspiration and analysis of cyst fluids, and histopathology.

Management

The treatment of inflammatory cysts depends on whether the involved non-vital tooth is to be retained. Conventional intra-canal endodontic treatment will often lead to the resolution of very small radicular cysts, but regular radiographic review is necessary until there has been complete resolution of the cyst. If, when the tooth has been root-filled, the cyst does not resolve, or if the cyst is of such a size that it is unlikely to resolve with endodontic treatment alone, surgery is indicated – either enucleation or marsupialisation.

The benefit of enucleation is that all the cyst tissue is available for histological examination and the cyst cavity will usually heal uneventfully with minimal aftercare. Enucleation is potentially problematic when the cyst involves the apices of adjacent vital teeth, as the surgery may deprive the teeth of their blood supply and render them non-vital.

Marsupialisation of the cyst may be an option in these cases, but this treatment requires considerable aftercare and good patient cooperation in keeping the cavity clean whilst it resolves. In order to keep the cavity open, a 'bung' or acrylic plug is usually inserted in the opening, often

attached to a denture or acrylic splint. The bung stops food collecting in the cavity, but the cavity must still be syringed by the patient after each meal. Marsupialised cyst cavities may take up to 6 months to close down to the extent of becoming 'self-cleansing'. The other disadvantage of marsupialisation is that not all the cyst lining is available to histopathological examination, and this may lead to misdiagnosis.

Odontogenic keratocyst (primordial cyst)

These cysts have generally been thought to arise from the dental lamina or its derivatives, but there is some suggestion that they may also arise from basal cells of the oral mucosa.

Clinical features

Keratocysts may be seen over a wide age range. Most involve the mandibular angle and may expand to occupy the major part of the mandibular ramus. They are often multilocular. They may resorb the cortical plates and expand into the soft tissues, may envelop unerupted teeth giving a dentigerous appearance, or they may displace teeth. Odontogenic keratocysts are generally painless, unless they become secondarily infected, and often grow to a large size before giving rise to symptoms.

Diagnosis

Diagnosis is on clinical grounds supported by imaging, aspiration and biopsy. The estimation of soluble protein level in aspirated cyst fluid is an aid to the diagnosis of keratocysts, since a protein level of less than 4 g per 100 ml suggests a keratocyst, whereas a value over 5 g per 100 ml suggests a radicular or follicular cyst, or rarely a cystic ameloblastoma. The demonstration of keratin squames in a cyst aspirate is virtually diagnostic of a keratocyst. The cyst lining usually has a characteristic appearance of a regular keratinised stratified squamous epithelium, commonly five to eight cell layers thick and without rete pegs. They are often multilocular. There is a well-defined basal layer predominantly of columnar, but occasionally cuboidal, cells. Desquamated keratin is often present within the cyst lumen and the fibrous wall is usually thin.

Management

Keratocysts tend to recur following removal; recurrence rates as high as 60% have been recorded. Although there is some dispute over the most appropriate treatment for keratocysts, all authors agree that the cyst lining should be meticulously removed. Gorlin syndrome should be excluded.

Small unilocular lesions should be thoroughly enucleated. When the cysts are large or multiloculated, excision with a margin of surrounding

bone may be more appropriate. Long-term clinical and radiographic follow-up of all keratocysts is mandatory as recurrences may occur many years after initial treatment.

Follicular (dentigerous) cyst

Follicular cysts arise by separation of the dental follicle from around the anatomical crown of an unerupted tooth. They may also form due to degeneration of the stellate reticulum, or an accumulation of fluid between the layers of the reduced enamel epithelium. The lining of follicular cysts typically consists of flattened stratified epithelium.

Clinical features

These cysts may grow to a large size, displace the tooth with which they are associated, or rarely cause resorption of adjacent teeth. They are most common in association with mandibular third molars and maxillary canines.

Diagnosis

Diagnosis is usually made by clinical and radiographic assessment – when the follicular space exceeds 5 mm from the crown it is likely that a cyst is present. However, odontogenic keratocysts and ameloblastomas may occasionally mimic the radiological appearances of follicular cysts. Aspiration may assist the diagnosis.

Management

Treatment may be either marsupialisation, allowing the tooth to erupt, or enucleation, with removal of the associated tooth.

Eruption cysts

Eruption cysts are considered as a minor soft tissue form of follicular cysts. They often burst spontaneously before eruption of the associated tooth, and only rarely require excision if impeding normal eruption.

Other odontogenic cysts

These cysts are uncommon. They can be subdivided into three groups: gingival cysts of adults and infants, and lateral periodontal cysts. The pathogenesis of these cysts is far from clear, gingival cysts of adults arise from epithelial rests in the gingivae, those in infants arise from remnants of the dental lamina. Lateral periodontal cysts arise from periodontal membrane alongside a vital tooth. Treatment of these cysts is generally by enucleation.

Odontogenic tumours

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Tumours of the dental tissues are classified according to the World Health Organisation (1992), mainly related to the tissues of origin and histopathological features.

Tumours consisting predominantly of epithelium originate from odontogenic epithelium, but it is uncertain whether this epithelium is derived from the enamel organ itself, the remnants of the dental lamina (cell rests of Serre) or Hertwig's root sheath (cell rests of Malassez), the epithelium of odontogenic cysts (particularly the dentigerous cyst) or from the oral mucosa.

Tumours composed of odontogenic connective tissue originate from the mesenchymal portion of the tooth germ, either from the dental papilla or the dental follicle.

Tumours of mixed origin consist both of odontogenic epithelium and mesenchyme, and during the period of active growth contain both ameloblastic epithelium and odontoblastic tissue but, when completely developed, consist principally of enamel, dentine, cementum or combinations thereof.

Enamel, dentine and their precursors are also present in a number of other lesions and their presence is usually indicated by inclusion of the word 'odonto' (e.g. ameloblastic fibro-odontoma, ontoameloblastoma, ameloblastic odontosarcoma).

Ameloblastoma

The ameloblastoma (adamantinoma) is a locally malignant odontogenic neoplasm.

Clinical features and diagnosis

Ameloblastomas are more frequent in males, usually after the age of 40 years. Some 80% are found in the posterior mandible. The tumour is not uncommon in black people compared to the low incidence in white people.

The initial detection of an ameloblastoma is likely to be a 'chance finding', but when the tumour is evident clinically there is a slow growing, painless, expansile swelling of bone. The lesion expands to produce progressive facial deformity and intraorally there may be evidence of malocclusion and mobile teeth. Eventually the bone is perforated and soft tissues involved. Radiographically, a monocystic or polycystic ('soap bubble') radiolucency is evident. Diagnosis is confirmed by histological examination of a biopsy specimen. Ameloblastomas are composed of epithelial cells arranged as a peripheral layer of ameloblast-like cells around a central area of cells resembling stellate reticulum. Two main histological types are

seen: follicular and plexiform types. In the follicular type, discrete islands (follicles) of epithelial cells are evident, whereas in the plexiform type the epithelium forms continuous anastomosing strands. Enamel formation is not evident, presumably because no odontogenic mesenchyme is present to give the inductive forces critical in the formation of dentine.

Histological variations occasionally seen in ameloblastomas include the presence of granular cells, squamous metaplasia and keratinisation, areas of calcification and variable degrees of vascularity. However, there appears to be little correlation between these histological patterns and the clinical course of the tumour. Features such as increased cellular pleomorphism and mitotic activity do, however, suggest that the lesions will behave more aggressively.

Management

Despite the ameloblastoma expanding rather than destroying bone, there is some local invasion of the surrounding bone. The treatment of choice, therefore, is surgical excision of the tumour together with removal of a margin of normal bone and retention of the lower border of the mandible if at all possible. Metastatic dissemination of the ameloblastoma is rare and usually occurs by aspiration to the lungs following longstanding local disease or previous surgical intervention.

Adenomatoid odontogenic tumour (adenoameloblastoma)

Clinical features and diagnosis

This tumour typically presents in the second and third decades, is more common in females than males and affects the maxilla more than the mandible. There is a propensity for the lateral incisor, canine and premolar regions.

Clinically, the lesion presents as a gradually increasing intrabony swelling which is occasionally painful. On radiographs, the tumour appears as a unilocular radiolucency and in some lesions there are radio-opaque foci. A clinical provisional diagnosis should include either a lateral periodontal cyst or a dentigerous cyst, particularly as, in the latter case, the tumour is sometimes associated with an unerupted tooth.

On histological examination, the tumour is encapsulated and consists of sheets and strands of epithelial cells arranged as convoluted bands and tubular structures. In the tubular structures, ameloblast-like cells are arranged radially around spaces containing a homogeneous eosinophilic material. The nature of this material is unknown, although suggestions have included pre-enamel, pre-dentine, amyloid and basement membrane material. Separate from the homogeneous material, foci of calcification frequently are evident throughout the lesion. The tumour contains little

intervening mesenchymal stroma, although cystic degeneration of this tissue is common.

Management

The adenomatoid odontogenic tumour is not locally invasive and shows no tendency to recur following conservative surgical excision.

Calcifying epithelial odontogenic tumour (CEOT; Pindborg tumour)

Clinical features and diagnosis

Calcifying epithelial odontogenic tumour (CEOT, Pindborg tumour) is rare and has been reported in all age groups (10–90 years), but manifests most commonly at approximately 40 years of age. It is found equally in males and females and is most frequent in the mandibular premolar–molar region. Rarely, it is extraosseous in more anterior parts of the mouth.

Clinically, there is a progressive painless swelling of the jaws.

Radiographically, the tumour usually appears as a radiolucency containing focal opacities. Approximately 50% of the lesions are associated with an unerupted tooth. Histological examination shows three distinct features:

- The lesion consists of sheets of epithelial cells (containing tonofilaments, desmosomes and hemi-desmosomes) which frequently are pleomorphic and which contain abnormal nuclei. In places, these cells are characterised by a clear cytoplasm, and hence have been termed 'clear cells'. Mitoses are rare.
- Amyloid, with its characteristic staining reactions (green birefringence with Congo red stain; positive fluorescence with thioflavine T), is evident throughout the tumour and is considered to be a product of the epithelial cells.
- Concentric masses of calcified tissues are present – often closely associated with the epithelial cells. It has been suggested that these may be a feature of the age of a tumour. Older lesions are characterised by more confluent calcified areas and by less prominent cellular features than young lesions.

Management

The CEOT is locally invasive and therefore is treated with surgical excision of the lesion plus a margin of normal bone.

Calcifying epithelial odontogenic cyst

Clinical features and diagnosis

Calcifying epithelial odontogenic cyst is an extremely rare lesion, which can occur at any age but most commonly presents in adults younger than

40 years. Either jaw of either sex may be affected, but the general site predilection is anterior to the first molar. Clinically, there is a slowly enlarging, painless swelling of the jaws which, on radiographic examination, commonly appears as a well-defined unilocular or multilocular radiolucency containing flecks of opacity. Embedded teeth and/or denticle-like structures are not infrequent findings.

Microscopically, the tumour may be solid or cystic. In cystic lesions, the cyst wall is lined by odontogenic epithelium resembling that in an ameloblastoma, with peripheral ameloblast-like cells in close association with more central cells comparable to the stratum intermedium and the stellate reticulum. In places, the epithelial cells undergo aberrant keratinisation to form large eosinophilic cells without a nucleus, termed 'ghost cells'. With further development, large masses of keratin accumulate and a foreign body giant cell reaction may be evoked if there is breakdown of the epithelial cyst lining. Foci of calcification and dentine-like material frequently are present throughout the specimen.

Management

Conservative enucleation of the lesion is rarely followed by recurrence.

Myxoma of the jaws

Clinical features and diagnosis

Myxoma of the jaws is derived from odontogenic mesenchyme and usually occurs in adolescents and young adults (10–40 years), manifests more frequently in females than males and presents in the posterior region of the mandible. The maxillary lesions that have been reported are characterised frequently by extensive involvement of the alveolar bone, the maxillary antrum and the zygomatic process. Clinically, the myxoma is an intrabony lesion which slowly expands the bony cortex and only perforates later. The lesion is rarely painful, but there may be loosening and displacement of the teeth. Radiographic examination shows a well-defined unilocular or multilocular ('soap bubble') radiolucency which may extend between the roots of the teeth and thus a scalloped margin is seen.

On microscopic examination of the biopsy specimen, spindle/stellate shaped cells are present in an intercellular mucoid stroma, sometimes containing nests of epithelial cells. Fibrous tissue and collagen are frequently evident throughout the lesion ('fibromyxoma'). There is widespread infiltration of the surrounding bone.

Management

Myxomas infiltrate and therefore should be treated with surgical excision of the tumour and removal of a margin of normal bone.

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- Compound composite odontomes consist of multiple small simple teeth embedded in fibrous connective tissue within a fibrous capsule.
- Complex composite odontomes consist of an irregular mass of all the dental tissues.

The classification, however, has little practical value because different areas of the same lesion can show 'compound' or 'complex' patterns and, furthermore, the classification bears no relationship to the prognosis.

Odontomes typically present in children and adolescents, are more common in females than males, and show a distinct predilection for the pre-molar-molar region of the mandible. Typically, they behave like teeth. They grow to a certain size and then tend to erupt with ulceration of the overlying oral mucosa. Alternatively, they may go unnoticed or, if located over the crown of an unerupted tooth, may prevent eruption. Radiographically, the lesions appear as small well-defined radio-opacities. The lesions are excised, but considerable mechanical difficulty may be encountered.

Enameloma

Rarely, disturbances in odontogenesis cause small deposits of enamel, termed enamelomas, between the roots of the first permanent molars.

Dentinoma

Focal deposits of dentine or osteodentine have been found overlying the crown of unerupted mandibular molar teeth in young adults and have been termed 'dentinomas'. The lesions are usually asymptomatic and appear as chance findings, as opacities on radiographic examination.

Cementoma

Cementum is normally deposited on the root of a tooth throughout life to compensate for occlusal wear; an excess of such physiological deposition is termed 'hypercementosis'. The common causes of hypercementosis are chronic periapical infection, a functionless tooth, a reaction to increased stress on the tooth, and Paget's disease. Hypercementosis is often symptomless and cause complications only during exodontia.

Alternatively, cementum may be deposited neoplastically, when the lesion is termed a 'cementoma'. These are uncommon but include the:

- cementoblastoma
- gigantiform cementoma
- periapical cemental dysplasia
- cementifying fibroma.

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ders. This has been confirmed and it is evident that a range of variants exist with antibodies directed against various hemi-desmosomal components or components of the lamina lucida. (Table 32.2):

- the mainly oral variant appears to be associated particularly with anti-integrin
- the mainly ocular variant, which also often involves the mouth, appears to be associated especially with anti-epiligrin.

Histologically, MMP is characterized by junctional separation at the level of the epithelial basement membrane zone giving rise to a sub-basilar split as in other forms of pemphigoid. The pathogenesis probably includes complement-mediated sequestration of leukocytes, with resultant cytokine and leukocyte enzyme release and detachment of the basal cells from the BMZ.

Clinical features

Pemphigoid has a wide clinical spectrum and heals with variable amounts of scar formation. The oral lesions seen in pemphigoid affect especially the gingivae and palate, and may include:

- Desquamative gingivitis; this is the most common oral finding and is characterized by erythematous, ulcerated, tender gingiva, usually in a patchy, rather than continuous distribution (Fig. 32.1). Sole involvement of the gingiva is not uncommon and is frequently misdiagnosed as inflammatory periodontal disease.
- Bullae or vesicles; intact blisters may be seen, but are not common, due to the incidental trauma of eating and speaking. Blisters are tense, may sometimes be blood-filled and can remain intact for several days, similar to those of angina bullosa haemorrhagica (localised oral purpura), often on the soft palate. Pressure on the blister may cause it to spread (Nikolsky sign).

Table 32.2 Antigens implicated in subepithelial disorders	
Disease	Antigen
Bullous pemphigoid	BP1 BP2*
Mucous membrane pemphigoid	BP2 Laminin 5,† 200 kDa, 168 kDa
Oral pemphigoid	Integrin
Linear IgA disease	97 kDa, 45 kDa
Epidermolysis bullosa acquisita	Type VII collagen
Toxic epidermal necrolysis	105 kDa
*Bullous pemphigoid	
†Also known as epiligrin, nicein, kalinin and BM600	



Figure 32.1 Mucosal pemphigoid commonly presents with desquamative gingivitis

- Persistent irregular erosions or ulcers after the blisters burst; these typically are covered with a yellowish fibrinous slough and surrounding inflammatory erythema, and thus resemble erosive lichen planus except that no white lesions are present. They may also resemble late lesions of pemphigus.
- Scarring, but only rarely in the mouth.

The majority of affected individuals with MMP have oral involvement only, but:

- genital involvement can be a source of great morbidity
- untreated ocular involvement can lead to blindness mainly due to conjunctival scarring (leading to entropion, symblepharon or ankyloblepharon)
- nasal lesions may bleed and crust
- laryngeal scarring may lead to stenosis
- skin blisters may rarely be seen
- internal malignancy may be present in some patients with anti-epiligrin pemphigoid.

Diagnosis

The oral lesions of pemphigoid may be confused clinically with pemphigus, angina bullosa haemorrhagica, dermatitis herpetiformis and linear IgA disease or, occasionally, erosive lichen planus, acquired epidermolysis bullosa, toxic epidermal necrolysis or erythema multiforme. Furthermore, the pemphigoid variants are indistinguishable clinically, by light microscopy and conventional immunostaining, one from another.

Therefore, biopsy of perilesional tissue, with histological and immunostaining examination can be essential to the diagnosis. The incisional biopsy specimen exhibits subepithelial clefting following staining with haematoxylin and eosin. Direct immunostaining is required to reveal the presence

of BMZ immune deposits. Indirect immunofluorescence is frequently negative and the levels of serum antibody, when detected with conventional techniques, are rarely of diagnostic significance.

Management

Few patients with pemphigoid have spontaneous remission, and thus treatment is usually indicated.

- Systemic manifestations must be given attention. Ocular manifestations have been reported in up to 20% of patients and, left untreated, can lead to blindness and thus an ophthalmological consultation is essential. Patients with MMP should also be questioned about the presence of other mucosal symptoms, which might indicate genital involvement. Patient information is an important aspect in management.
- The majority of cases respond well to topical corticosteroids or tacrolimus, which are also the usual treatment for desquamative gingivitis and may be effective if used in a vacuum-formed custom tray or veneer worn during sleep.
- The management of desquamative gingivitis associated with pemphigoid should also include oral hygiene improvement, as secondary infection may inhibit healing.
- Severe pemphigoid may need to be treated with dapsone or immunosuppression using azathioprine or systemic corticosteroids, but this is of variable benefit and/or can give rise to serious adverse effects.

Patient information sheet

PEMPHIGOID

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- This is an uncommon condition.
- The cause is unknown but it may be immunological.
- It is not thought to be inherited.
- It is not thought to be infectious.
- It occasionally affects the skin or other sites.
- It usually has no long-term consequences.
- Blood tests and biopsy are often required.
- Pemphigoid may be controlled but rarely cured with medicines.
- Useful website: <http://www.dent.ucla.edu/pic/members/MMP>.

Websites

PDFFREE.COM/WWW.AAODA.ORG/INDEX.HTML

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Pemphigus

Introduction

Pemphigus is a group of potentially life-threatening chronic autoimmune diseases characterised by epithelial blistering affecting mucocutaneous surfaces, the term being derived from the Greek *pemphix* (bubble or blister).

There are several variants of pemphigus with different autoantibody profiles and clinical manifestations. The main types are:

- Pemphigus vulgaris: this includes an uncommon variant – pemphigus vegetans. The main antigen in pemphigus vulgaris is desmoglein (Dsg) 3, a constituent of epithelial intercellular cement.
- Pemphigus foliaceus: this includes the uncommon variant pemphigus erythematosus (Senear-Usher syndrome). The main antigen in pemphigus foliaceus is Dsg 1.

Pemphigus vulgaris is the most common pemphigus variant, and the form usually responsible for oral lesions.

Pemphigus vulgaris

Incidence

Pemphigus vulgaris is a rare disease.

Age

Pemphigus vulgaris is found mainly in middle-aged and elderly patients.

Sex

There is a female predisposition.

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- mouth
- pharynx
- larynx
- oesophagus
- rectum
- nose
- conjunctiva
- anogenital region.

Pemphigus vulgaris often begins with blister formations (bullae) occurring in the mouth and on the scalp. The blisters are soft and are easily broken. The Nikolsky sign (the spreading of a blister by pressure) is positive.

Oral lesions in pemphigus vulgaris:

- are common
- may be an early manifestation
- may be the sole manifestation for a considerable time
- are vesiculobullous, but readily rupture, new bullae developing as the older ones rupture and ulcerate
- form erosions, which are irregular and initially red with a whitish surround (Fig. 33.1), but become yellowish
- are seen mainly on the:
 - soft palate and posterior hard palate
 - buccal mucosa

Table 33.1 Antibodies to desmogleins in pemphigus vulgaris

Pemphigus vulgaris lesions	Dsg 3	Dsg 1
Mucosal mainly	+	-
Mucocutaneous	+	+



Figure 33.1 Pemphigus; typical irregular early red lesions

- lips
- gingiva, where lesions usually comprise severe desquamative or erosive gingivitis; flaps of peeling tissue with red erosions or deep ulcerative craters are seen, mainly on the attached gingivae
- are almost invariably followed by involvement of the skin or, occasionally, other epithelia such as the oesophagus in the absence of systemic treatment.

Diagnosis

- Diagnosis of an autoimmune bullous disease should be suspected when there is no clear history of exposure to a drug or allergen or when other studies for infectious origins, such as herpes or impetigo, are negative.
- The differential diagnosis includes:
 - pemphigoid
 - erythema multiforme and toxic epidermal necrolysis
 - pyostomatitis vegetans
 - paraneoplastic pemphigus
 - IgA pemphigus (intraepithelial IgA pustulosis)
 - pemphigus associated with inflammatory bowel disease.
 Other types of pemphigus, such as pemphigus foliaceus and erythematosis and pemphigus vegetans, which only rarely affect the oral mucosae.
- To differentiate these bullous diseases, a careful history and physical examination are important, but biopsy is mandatory.
- Biopsy of perilesional tissue, with histological and immunostaining examination are essential.
- Serum should be collected for titres of antibody to epithelial intercellular cement, which may help guide treatment. Serum autoantibodies to Dsg are best detected using both normal human skin and monkey oesophagus by enzyme-linked immunosorbent assay.

Management

Before the introduction of corticosteroids, pemphigus vulgaris typically was fatal mainly from dehydration or secondary systemic infections. Pemphigus vulgaris remains a life-threatening disorder, though current treatment, largely based on systemic immunosuppression, has significantly reduced the mortality to about 10%. Patient information is thus an important aspect in management.

Oral lesions are persistent, and are often recalcitrant even when cutaneous lesions are controlled by treatment. Hence, systemic corticosteroids (e.g. prednisolone at least 60 mg/day) are essential, unless there are only

localised oral lesions, when topical corticosteroids or intralesional corticosteroids may suffice for a time (Table 33.2). Once under control, the dosage of prednisolone can be tapered or adjuncts added. Adjuncts or alternatives include:

- azathioprine,
- ciclosporin

Table 33.2 Monitoring protocol for patients with pemphigus on systemic corticosteroid therapy during the first 3 months of therapy*

Daily	Weekly	Monthly
Diet low in sodium and carbohydrate	Clinical oral examination	Titre of serum antiepithelial antibodies
Blood pressure estimation	Body weight estimation	–
Recording of symptomatology	Recording of symptomatology	Haematological examination for first month, then every 15–30 days

*Bone densitometry every 6 months.

Patient information sheet

PEMPHIGUS

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- This is a rare condition.
- It is an immunological disease, the immune reaction damaging the skin.
- It is most commonly seen in persons from around the Mediterranean.
- It is not usually inherited.
- Pemphigus is not known to be infectious.
- It affects the mouth, skin and other sites.
- Uncontrolled it is a very dangerous condition.
- Blood tests and biopsy are usually required.
- Strong drugs such as steroids are normally needed to control pemphigus.
- Useful website: <http://www.pemphigus.org>
- Advice is available from:
 - Pemphigus Vulgaris Network, Flat C, 26 St. German's Road, London SE23 1RJ
 - National Pemphigus Vulgaris Foundation, PO Box 9606, Berkeley, CA 94709-0606, USA. Tel. (+1) 510 527 4970.

- cyclophosphamide
- others, such as gold, dapsone, chlorambucil, levamisole and immunoglobulins.

It is possible to eventually induce complete and durable remissions in most patients, permitting systemic therapy to be safely discontinued without a flare in disease activity. The proportion of patients in whom this can be achieved increases steadily with time, and therapy can be discontinued in approximately 75% of patients after 10 years.

Websites

The National Pemphigus Foundation (drugs used in treating pemphigus):
<http://www.pemphigus.org/drugs.htm>

The National Pemphigus Foundation (symptoms and treatment of pemphigus):
<http://www.pemphigus.org/pemphigus.htm>

American Autoimmune Related Diseases Association, Inc.:
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34

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Sjögren Syndrome

Introduction

Sjögren syndrome (Gougerot-Sjögren syndrome (SS)) is the association of dry mouth and dry eyes with lymphoid infiltrates in exocrine glands, and autoantibodies (Fig. 34.1). It has two main forms, which differ in certain features (Table 34.1):

- Primary Sjögren syndrome (SS-1), in which Sjögren syndrome appears by itself, in the absence of a connective tissue disease. This is uncommon and sometimes termed 'sicca syndrome', but the latter is also used non-specifically.
- Secondary Sjögren syndrome (SS-2), which comprises dry eyes and dry mouth together with a connective tissue or autoimmune disease, is

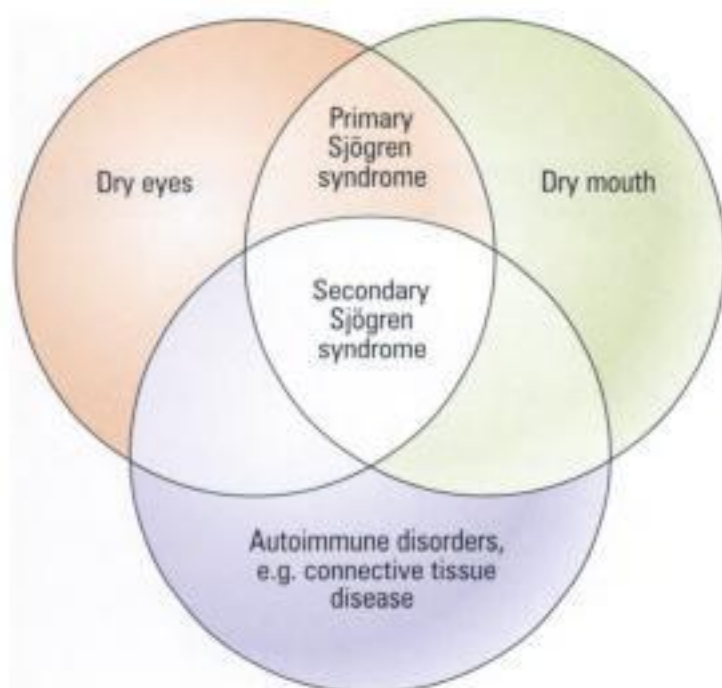


Figure 34.1 Sjögren syndrome

more common. The association is usually with (in descending order of frequency):

- rheumatoid arthritis (RA)
- systemic lupus erythematosus
- polymyositis
- scleroderma
- primary biliary cirrhosis.

Incidence

Sjögren syndrome itself is uncommon, although the very rarity may lead to underdiagnosis. However, a subjective feeling of dry mouth (xerostomia) is common, although reduced salivary flow (hyposalivation) is not always confirmed by objective studies. Indeed, in the older age groups, 16–25% complain of xerostomia – usually caused by drugs.

Age

Sjögren syndrome can affect any age, but the onset is most common in middle-age or older.

Sex

The majority of patients are women

Geographic

No known geographic incidence.

Table 34.1 Sjögren syndrome: comparison of subtypes

Feature	SS-1	SS-2
Connective tissue disease	–	+
Oral involvement	More severe	Less common
Ocular involvement	More common	Less common
Recurrent sialadenitis	More common	Less common
Lymphoma	More common	Less common
Main serum autoantibody	SS-B	SS-A

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- Difficulties in controlling dentures.
- **Difficulties in speech:** there may be a clicking quality of the speech as the tongue tends to stick to the palate.
- Difficulties in swallowing.
- Swollen salivary glands (Fig. 34.3): enlargement of the major salivary



Figure 34.2 Sjögren syndrome showing dry mouth



Figure 34.3 Sjögren syndrome showing salivary swelling

glands may affect up to about one-third or more of patients at some time.

- Unpleasant taste or loss of sense of taste.
- Connective tissue disease such as rheumatoid arthritis or other connective tissue disease is typically longstanding and should be clinically obvious. The connective tissue disease in secondary Sjögren syndrome usually precedes the onset of dry eyes and dry mouth, and therefore patients presenting with dry eyes and dry mouth alone probably have primary Sjögren syndrome, unless a connective tissue disease manifests within about 1 year.
- Other complaints can include:
 - rash
 - dry vagina
 - bruising, bleeding and purpura
 - numbness.

Oral and salivary gland examination is important. The mouth may appear dry, and on examination there may be:

- lack of salivary pooling
- frothiness of saliva and absence of frank salivation from major gland duct orifices
- tendency of the mucosa to stick to a dental mirror
- in advanced cases an obviously dry and glazed mucosa
- a characteristic tongue appearance; lobulated, usually red, surface with partial or complete depapillation.

Complications

- Candidiasis is common and may cause soreness and redness of the oral mucosa or angular cheilitis.
- Dental caries tends to be severe, affect smooth surfaces, and is difficult to control.
- Ascending (suppurative) sialadenitis is a hazard.
- Salivary gland enlargement is not uncommon in Sjögren syndrome. It is:
 - usually caused by the Sjögren syndrome inflammatory process and is mild
 - intermittently caused by bacterial ascending infection
 - occasionally massive and associated with enlargement of the regional lymph nodes, a condition called 'pseudolymphoma'
 - rarely due to lymphoma which may result from the B-cell lymphoproliferation (lymphoproliferation in the mucosal-associated lymphoid tissue (MALT lymphoma)).

Diagnosis

Specialist referral is warranted since investigations may be needed, and the differential diagnosis may include:

- Viral infections:
 - hepatitis C virus
 - HIV
 - HTLV-1
 - EBV.
- Sarcoidosis.
- Glandular deposits in:
 - haemochromatosis
 - lipoproteinaemias
 - amyloidosis.
- Lymphomas.

The diagnosis of Sjögren syndrome is mainly on the history, clinical examination and investigation, including:

- ocular symptoms
- oral symptoms
- ocular signs
- autoantibodies
- salivary gland involvement
- histopathology.

The American–European diagnostic criteria (revised) for Sjögren syndrome are shown in Table 34.3.

Eye examination

Examination of the eyes by a Specialist is most important (see Table 34.3).

Autoantibodies and other blood tests

Autoantibody assays can be extremely helpful in diagnosis, and are readily available, inexpensive and fairly non-invasive. SS-A (Ro) and SS-B (La) antibodies are found especially in primary Sjögren syndrome, may have diagnostic value in patients with unexplained parotid swelling and may antedate clinical evidence of Sjögren syndrome by months or years.

- Blood tests may be indicated to examine for SS-A and SS-B and to:
 - assess erythrocyte sedimentation rate or plasma viscosity
 - exclude anaemia

Table 34.3 American–European diagnostic criteria for Sjögren syndrome*

Sjögren syndrome is diagnosed if four of the following six are positive (especially histopathology and serology) or if there are ocular symptoms or oral symptoms plus any two of the other four:

- ocular symptoms
- oral symptoms
- ocular signs
- histopathology
- salivary gland involvement
- autoantibodies.

Ocular symptoms

At least one of these Daily persistent troublesome dry eyes for >3 months
 Recurrent sensation of sand or gravel
 Need to use teardrops >3 times daily

Oral symptoms

At least one of these Daily feeling of dry mouth >3 months
 Recurrent or persistently swollen salivary glands as adult
 Frequently drink liquids to aid swallowing dry foods

Ocular signs

At least one of these Schirmer <5 mm in 5 min
 Rose Bengal score >4

Histopathology Focus score >1 on LSG[†]

Salivary gland involvement

At least one of these Scintigraphy – reduced concentration/uptake/excretion abnormal
 Sialography – diffuse sialectasis
 Unstimulated whole salivary flow <1.5 ml in 15 min

Serum autoantibodies

At least one of these SS-A (Ro)
 SS-B (La)

*See Vitali et al (2002) for detail

[†]Focus = cluster of 50 or more lymphocytes in a labial salivary gland (LSG)
Focus score = average number of foci in a 4 mm² area

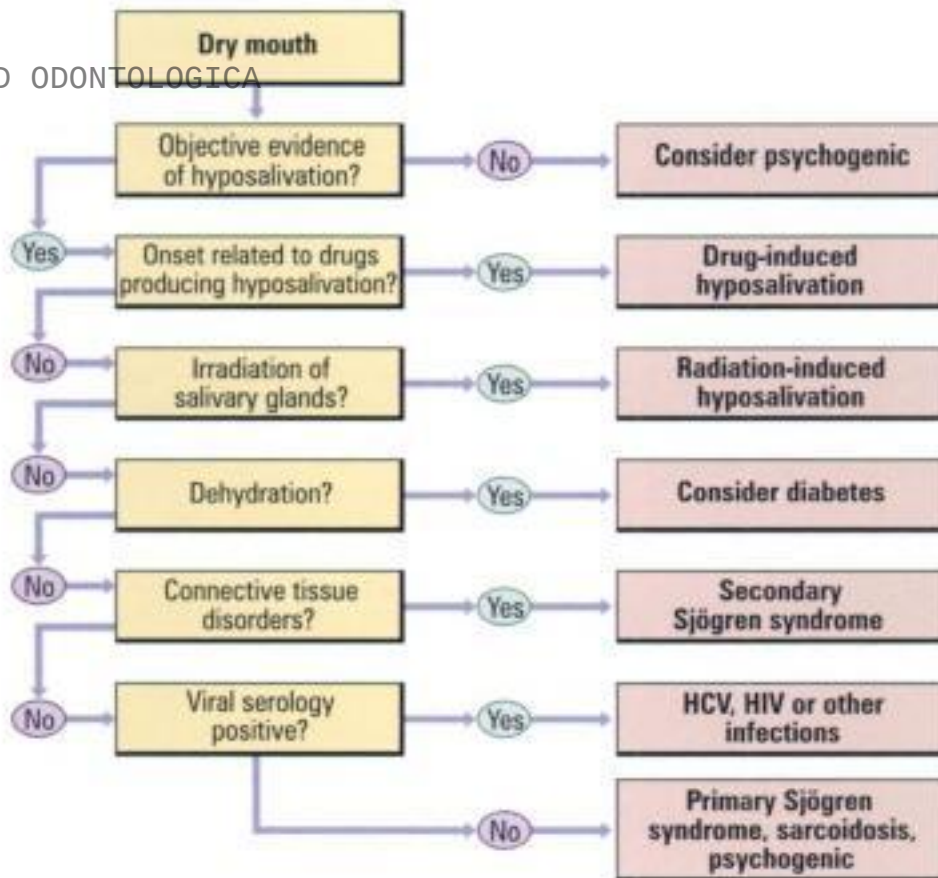


Figure 34.4 Algorithm for dry mouth

- examine IgA immune complexes
- exclude similar syndromes seen in infection with hepatitis C virus, EBV, HTLV-1 or HIV.

Salivary gland examination

Salivary gland examination, functional studies and biopsy may be indicated (Tables 34.3 to 34.5, Figs 34.4 to 34.6).

Salivary flow measurements (sialometry)

These are relatively simple and non-invasive, but are non-specific, and not especially sensitive. Objective evidence of diminished salivary flow in Sjögren syndrome include a:

- Decreased resting secretion rate of whole saliva <1.5 ml in 15 min: this is more closely associated with symptoms of xerostomia than are stimulated flow rates. The test should be standardised by being carried out: after overnight fasting; first thing in morning; no food or drink for at least 1 hour before the test; no smoking for at least 1 hour before the test; and with the patient being asked to dribble all their saliva into a measuring container for 15 min.

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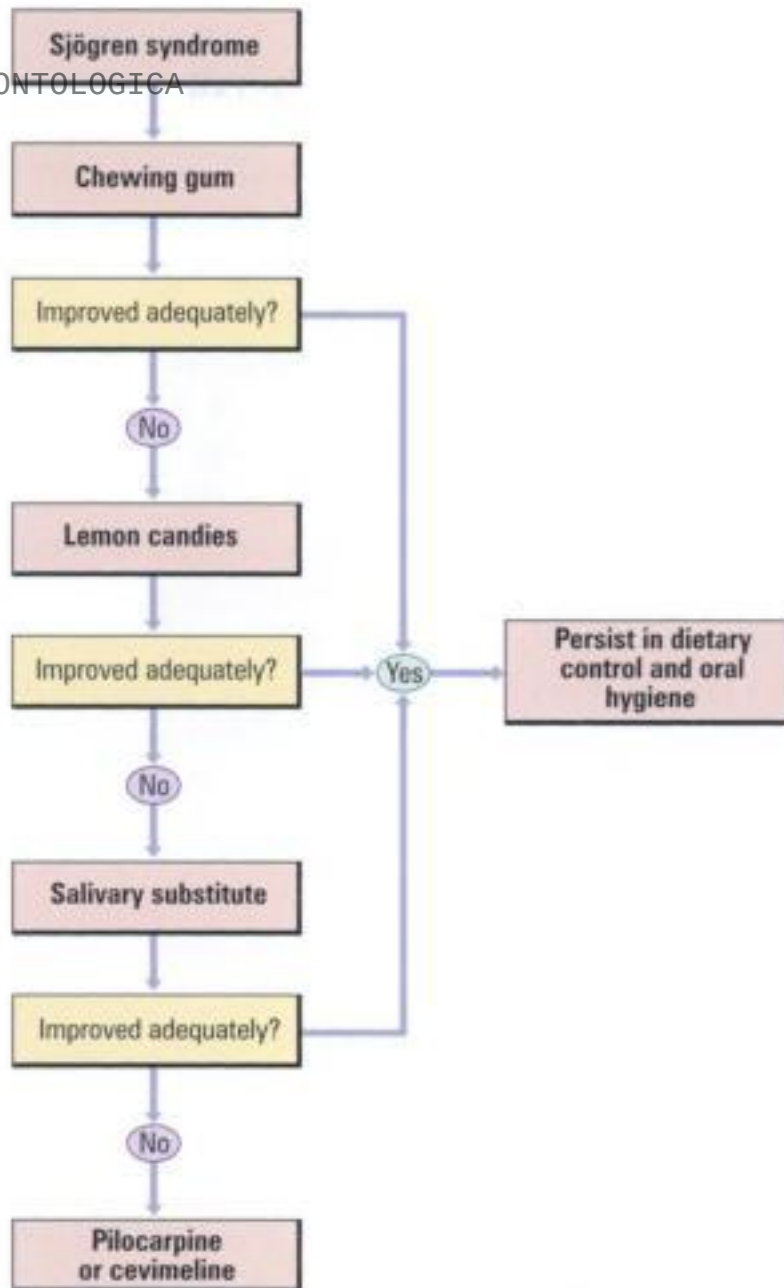


Figure 34.6 Algorithm for Sjögren syndrome management

Salivary gland biopsy

Biopsy of salivary glands can be useful in the diagnosis of Sjögren syndrome. Biopsy of major glands involves a skin incision and slight possibilities of facial nerve injury, scarring and salivary fistula. Therefore minor salivary glands are usually biopsied.

Minor glands in the palate and lower lip are accessible, but the latter site is preferred both from the aspects of patient comfort and access for the operator and also because the extent and pattern of histopathological changes on labial salivary gland (LSG) biopsy correlate with those in parotid and submandibular glands.

The LSG biopsy technique involves: local analgesia; simple linear incision in the lower labial mucosa just to one side of the midline; at least five

lobules of LSG are blunt dissected out and removed; and one or two sutures are placed to ensure haemostasis. There are few adverse effects except occasional minor hypoaesthesia.

Focal sialadenitis is the characteristic histopathological feature. LSG histology, if used with a focus score (FS) provides a reproducible and objective evaluation of severity of inflammation. Other features such as fibrosis or fatty atrophy, duct dilatation and hyperplasia, however, are non-specific. A focus is defined as an aggregate containing 50 or more mononuclear cells: the FS is the number of such aggregates in each 4 mm² area. The mononuclear cells are predominantly T-helper inducer cells. The FS is reliable only where gland lobes with acinar atrophy and interstitial fibrosis are excluded, and where an adequately large specimen is examined. The threshold FS generally used for diagnosis of Sjögren syndrome is one focus per 4 mm², though others use slightly higher thresholds. Focal sialadenitis in an adequate LSG biopsy (at least 4–5 lobules) appears to be the most disease-specific and sensitive diagnostic method for Sjögren syndrome.

Sialography

Sialography has the following characteristics:

- specificity is low
- time-consuming
- may be painful
- may produce hazards, such as granulomatous reactions or infection
- shows sialectasis (this is the most typical finding, it is most sensitive using oil-based contrast media and is seen particularly in parotid glands and may correlate with histological scores and scintigraphy).

Table 34.5 Salivary investigations in Sjögren syndrome		
Investigation	Typical findings	Comments
Sialometry	Reduced	Non-specific, but readily available
Sialography	Sialectasis	Non-specific, but often available
Scintigraphy	Reduced radionuclide uptake	Non-specific, but expensive
Salivary gland biopsy	Focal lymphocytic infiltrate Acinar atrophy Fibrosis	More specific

Salivary scintiscanning

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Salivary scanning (scintigraphy) has the following characteristics:

- shows diminished radionuclide uptake and spontaneous secretion, or secretion following citric acid or pilocarpine stimulation
- is relatively non-invasive
- examines both parotid and submandibular glands simultaneously
- changes correlate with sialographic, flow rate and LSG histological changes but are non-specific
- quantitative registration of uptake and secretion phases with correction for vascular background might improve the diagnostic and monitoring value of salivary scintigraphy.

Ultrasonography

This is proving to be a useful method for evaluating salivary gland involvement in Sjögren syndrome and may replace other diagnostic techniques, such as sialography or salivary scintigraphy.

Magnetic resonance imaging

This can be helpful in showing soft tissue changes.

Sialochemistry

- Analysis of salivary composition (sialochemistry) for the diagnosis and monitoring of salivary disease has had some enthusiastic proponents but has been of no practical value. It could prove to be of value in monitoring the disease process in view of the non-invasive nature. The diagnostically and prognostically most promising recent sialochemical findings have been of raised levels of:
 - lactoferrin
 - β_2 microglobulin
 - interleukin-6
 - lysozyme
- sodium, chloride, albumin, lactoferrin, IgA and IgG (however, these are non-specific and rarely correlate with salivary flow or histological changes).

Management

- Patient information is an important aspect in management.
- Any connective tissue or other disorders should be treated by a physician.
- Few patients with Sjögren syndrome have spontaneous remission, and thus treatment of symptoms is indicated. Recently there have been

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- It is wise for the patient to avoid: mouth-breathing; any drugs that may produce xerostomia (e.g. tricyclic antidepressants); alcohol (including in mouthwashes); smoking; caffeine (coffee, some soft drinks); dry foods such as biscuits (or moisten in liquid first); spicy foods; and oral healthcare products containing sodium lauryl sulphate, which may irritate the mucosa.
- Salivation may be stimulated by using: chewing gums (containing xylitol or sorbitol, not sucrose); diabetic sweets; cholinergic drugs that stimulate salivation (sialogogues) should be used by the specialist as discussed in Chapter 6; and transglossal electrical stimulation.
- Salivary substitutes may help symptomatically. Various apart from water are available, including: methylcellulose; Saliva Orthana and Oralbalance are particularly useful since they contain fluoride (see Appendix 2) and mucin.
- Complications should be avoided or managed by:
 - avoiding sugary foods
 - keeping the mouth clean
 - using fluorides
 - using mouthwashes of chlorhexidine.
- Dental caries is best controlled by dietary control of sucrose intake, and the daily use of fluorides as toothpastes, mouthwashes and gels (1% sodium fluoride gels or 0.4% stannous fluoride gels).
- Candidiasis may cause soreness or burning and thus should be treated with antifungals until there is neither erythema nor symptoms. Topical antifungals in liquid form such as nystatin or amphotericin suspension are effective and acceptable since the mouth is dry. Other preparations such as miconazole or fluconazole are also effective. Dentures should be left out of the mouth at night and stored in sodium hypochlorite solution, chlorhexidine or benzalkonium chloride to disinfect. An antifungal such as miconazole gel or amphotericin or nystatin ointment should be spread on the denture before reinsertion
- Bacterial sialadenitis needs treating with a penicillinase-resistant antibiotic such as flucloxacillin.
- Lymphomas; an oncological opinion is indicated; chemotherapy may be required.

Websites

Arthritis Link: <http://www.arthritislink.com/arthhlinks.htm>

Sjögren's Syndrome Foundation: <http://www.sjögrens.org>

British Sjögren's Syndrome Association:

<http://ourworld.compuserve.com/homepages/bssassociation>

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Age

This disorder affects young people mainly, typically teenagers or young adults.

Sex

Most patients are females between 20 and 30 years of age.

Geographic

No known geographic incidence.

Predisposing factors

Trauma and stress appear to predispose.

Aetiology and pathogenesis

Hypotheses are many, but facts are few. TMJ dysfunction is a symptom complex of multifactorial aetiology which almost certainly represents a psychological response to stress that becomes chronic through increasing muscle tension affecting the muscles of mastication (mainly the temporalis, masseter and pterygoid muscles).

Trauma

- Trauma including from road accidents, sports injuries, fights and dental extractions can be followed occasionally by TMJ dysfunction.
- TMJ dysfunction can be secondary to microtrauma and subsequent muscle hyperactivity, which can result from prolonged mouth opening, as in dental treatment sessions. Other causes of prolonged and/or excessive mandibular opening: for example general anaesthesia, choir singing or wind instrument playing, or parafunctions such as day-time jaw clenching or night-time tooth grinding (bruxism), and habits such as chewing a pen, can also lead to TMJ dysfunction.

Muscle hyperactivity

- Psychological stress can cause muscle hyperactivity.
- Muscle hyperactivity has been demonstrated in TMJ patients during activities such as school examinations and watching horror films.
- 50–70% of patients (twice as common as controls) have experienced stressful life events in the 6 months before onset. These problems con-

cerning work, money, health, loss and interpersonal relationships, probably have a causative role by inducing anxiety which then produces increased jaw muscle activity.

- The two heads of the lateral pterygoid muscle have separate actions, the lower contracting during mouth opening, the superior head contracting during closing, to steady the meniscus as it moves back with the condyle into the glenoid fossa. During closing the lower head is electromyographically silent. In TMJ dysfunction patients, the lower head of the lateral pterygoid muscle contracts during the closing phase (when it should be relaxed). It has been suggested that anterior displacement of the TMJ meniscus, perhaps from a tear of the posterior capsule, prevents the superior head from acting effectively. The lower head perhaps attempts to help stabilise the meniscus. This might explain why this muscle is tender on palpation in TMJ dysfunction patients. Anterior displacement of the meniscus has been demonstrated by TMJ arthrography and found at operation in some TMJ dysfunction patients. Patients may be classified as having: no meniscus displacement; anterior displacement with reduction (excessive forward movement during opening which relocates on closing); and anterior displacement without reduction, when the meniscus remains anterior to the condyle in a buckled-up fashion, such that there is a reduced joint space and the articular surface of the condyle is close to the articular surface of the glenoid fossa. This latter situation predisposes to subsequent osteoarthritis.

Possible dental causes

Abnormalities in the dental occlusion are controversial as causes of TMJ dysfunction. There is no neurophysiological evidence to support a primary aetiological role for the occlusion in TMJ dysfunction and many people with gross malocclusions have no TMJ dysfunction. There is no significant difference in the incidence of occlusal abnormalities between TMJ dysfunction patients and control subjects, nor is there any evidence for a relationship between orthodontic treatment (or the wearing of orthodontic headgear) and TMJ dysfunction.

Clinical features

Symptoms are highly variable, but dysfunction is characterised by:

- Recurrent clicking in the TMJ: clicking occurs either on attempted opening or closing. Often the click allows the completion of that phase of mandibular movement. Sometimes clicking ceases and the jaw locks either open or closed. Clicks are not diagnostic, since they are common

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Table 35.1 Helkimo indices

Anamnestic index, Ai	Symptoms	Clinical dysfunction index, Di	Dysfunction
Ai 0	None	Di 0	None
Ai I	Mild: TMJ sounds; feelings of stiffness of the jaws	Di I	Mild
Ai II	More severe: difficulty in opening the mouth wide; locking; fixation; pain on movement; facial and jaw pain	Di II Di III	Moderate Severe

be revealed by radiography. Indeed, radiographic changes are uncommon and arthrography, computed tomography (CT) or magnetic resonance imaging (MRI) are rarely indicated. The condylar position as seen on radiography is unreliable for diagnosis and does not indicate meniscus displacement.

Radiography is not, therefore, recommended for diagnosis unless there is:

- a history of trauma
- significant limitation of movement
- sensory or motor alteration
- a possibility of organic joint or other disease.

CT is then most accurate.

Other diagnostic procedures

There is no reliable scientific evidence to support the regular use of other suggested 'aids' such as:

- jaw tracking (mandibular kinesiography)
- electromyography
- electrovibratography
- sonography
- thermography.

Management

Patient information is an important aspect in management. TMJ dysfunction appears not to lead to long-term joint damage and some patients have

Patient information sheet**TEMPOROMANDIBULAR PAIN-DYSFUNCTION**

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- This is a common condition.
- It appears to be related to stress, damage or habits involving the teeth and joints.
- It is not inherited.
- There are no serious long-term consequences; arthritis does not result.
- The symptoms usually clear spontaneously after some months.
- Various treatments such as rest, exercises, drugs, splints or adjustments to the teeth may help.
- Useful websites:
http://www.aaop.org/TMD/info_intro.htm
<http://www.tmjd.com>.

spontaneous remission: thus treatment is not always indicated. There is no indication, for example, for attempting treatment for TMJ clicks that are otherwise symptomless. However, in persons who complain of pain, treatment may be worthwhile. The level of placebo response and the response from reassurance is impressive and conservative measures are at least partially successful in up to 90%, usually within 6 months. The aims of treatment are to:

- control immediate pain
- lower psychological stress
- eliminate TMJ damage.

Possible treatments

There is a wide range of treatments offered for TMJ dysfunction, including physical, medical, psychological and surgical approaches. These include:

Physical treatments

Dental treatments include:

- occlusal adjustments
- occlusal reconstruction
- occlusal covers (e.g. polythene vacuum-formed cover)
- immobilisation.

Patient information sheet**TEMPOROMANDIBULAR PAIN–DYSFUNCTION: FOUR STEPS TO MANAGE JAW PAIN**

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- Rest yourself and your jaw:
 - relax and practice stress reduction
 - exercise regularly
 - eat soft foods and avoid hard, crusty foods like nuts or hard bread or those that need chewing a great deal
 - chew on your back teeth, not the front ones
 - eat small bites
 - sleep on your side.
- Avoid joint or muscle damage by avoiding:
 - contact sports (wear a mouthguard if you must play contact sports)
 - excessive jaw use in yawning, grinding and clenching
 - chewing gum
 - habits such as biting finger nails, pens and pencils or lip
 - long dental appointments or general anaesthesia
 - cradling the telephone between head and shoulder
 - wind instrument playing.
- Reduce muscle pain with analgesics and by applying:
 - cold packs for 10 minutes every 3 hours for 72 hours after injury
 - hot packs for 20 minutes every 3 hours to uninjured joints/muscles.
- Re-educate the jaw opening:
 - open your mouth with a hinge movement
 - exercise your jaw twice daily, opening 5 times in front of a mirror, ensuring the jaw opens vertically downwards without deviating sideways
 - exercise your jaw three times daily for 5 timed minutes:
 - close your mouth on the back teeth
 - put the tip of your tongue on the palate behind your front teeth
 - move the tongue back across the palate as far as it will go
 - keep the tongue in this position with the teeth closed for 10 seconds
 - open your mouth slowly until the tongue starts to leave the palate
 - keep that position for 10 seconds
 - close your mouth
 - repeat over 5 minutes.

Muscle treatments include:

- rest
- heat
- ultrasound

- transcutaneous electrical nerve stimulation
- muscle exercises
- mandibular orthopaedic repositioning appliance.

Medical treatments

- Non-steroidal anti-inflammatory drugs
- local analgesics
- muscle relaxants
- tranquillisers (benzodiazepines, tricyclics)
- antidepressants
- intra-articular steroids.

Psychological treatments

Psychological treatments include:

- psychiatric treatment
- group therapy
- behaviour modification/biofeedback
- hypnosis.

Surgical treatments

Surgical treatments include:

- condylotomy (rarely, high condylar shave; high partial condylectomy indicated)
- capsular rearrangement
- silicone or Teflon implants
- auriculotemporal nerve section.

Treatment regimens

Although in the past it has been accepted practice to relieve obvious occlusal interferences and to correct prosthetic discrepancies such as an incorrect vertical dimension, any possible benefits from major occlusal alterations must be set against a high placebo response and the important role of reassurance.

A typical treatment regimen includes:

- Rest.
- Avoidance of trauma, wide opening and abnormal habits.
- Analgesics; non-steroidal anti-inflammatory agents such as aspirin can be helpful. Injection of local analgesics into painful sites, or the spraying of coolants such as trichlorofluoromethane onto the areas, can ease pain and break the cycle.

- Muscle relaxants such as clonazepam 0.25 mg/day or baclofen 10 mg three times daily can provide relief.
- Warmth, massage and remedial jaw exercises to control discomfort.

If these are insufficient, it may be helpful to use:

- Plastic splints on the occlusal surfaces (occlusal splints). It is unclear how these function, but they increase the vertical dimension, may reduce joint loading, eliminate faulty occlusal interferences, and probably most importantly provide cognitive awareness of damaging oral habits and engender a placebo effect. In any event, at least 40% benefit symptomatically, especially from hard splints.
- Ultrasound.
- Biobehavioural modalities (psychotherapy, biofeedback, relaxation), anxiolytic agents or antidepressants. These include:
 - diazepam 2 mg three times daily
 - lorazepam 1 mg/day
 - alprazolam 0.25 mg three times daily.

The remaining subgroup of 5–10% of patients may need treatment for prominent psychological problems by either medication or psychiatric therapy. The very small minority of patients who fail to respond to the above measures may require local corticosteroid or sclerosant therapy. Surgery may be required for the very small number of remaining non-responders, especially those with obvious intra-articular pathology (osteoarthritis).

Websites

TMJ Association: <http://www.tmj.org/home.asp> <http://www.entnet.org/tmj.html>

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Trigeminal and other Neuralgias

Introduction

Sensory innervation of the mouth, face and scalp depends on the fifth cranial (trigeminal) nerve, so that disease affecting this nerve can cause orofacial pain or sensory loss, or indeed both, sometimes with serious implications. The term 'neuralgia' means pain in a nerve. Trigeminal neuralgia (TN) is a disorder of the trigeminal nerve that causes episodes of unilateral intense, stabbing, electric shock-like pain in the areas of the face where the branches of the nerve are distributed – lips, eyes, nose, scalp, forehead, upper jaw or lower jaw. TN is not fatal, but it is universally considered to be one of the most painful afflictions known.

Trigeminal neuralgia with no obvious neurological cause

This is also known as idiopathic trigeminal neuralgia, benign paroxysmal trigeminal neuralgia, trigeminal neuralgia and tic douloureux.

Incidence

Uncommon, probably about 4 cases per 100,000 population, although TN is the most common neurological cause of facial pain.

Age

TN onset is mainly in the 50–70 year age group.

Sex

TN is slightly more common in women.

Geographic

There is no known geographic incidence.

Predisposing factors

No predisposing factors have been identified but emotional or physical stress can increase the frequency and severity of attacks.

Aetiology and pathogenesis

The cause is unclear, but one hypothesis is that there may be compression around the trigeminal root in the posterior cranial fossa, possibly due to a cerebral blood vessel becoming atherosclerotic, and therefore less flexible, and then pressing on the roots of the trigeminal nerve, causing neuronal discharge.

Clinical features

TN affects mainly the second and third divisions of the trigeminal nerve. TN has the following main characteristics as defined by the International Headache Society:

- Paroxysmal attacks of facial pain which last a few seconds to less than 2 minutes; occurring especially in the morning, rarely at night.
- Pain has at least four of the following characteristics:
 - a distribution along one or more divisions of the trigeminal nerve
 - a sudden intense, sharp superficial, stabbing or burning quality
 - the pain intensity is severe
 - precipitation from trigger areas or by certain daily activities, such as eating, talking, washing the face, shaving or cleaning the teeth
 - the patient is usually entirely asymptomatic between paroxysms, but some patients experience a dull ache at other times.
- There is no neurological deficit.
- The attacks are stereotyped in the individual patient.
- Exclusion of other causes of facial pain by history, physical examination and special investigations when necessary.

A less common form of the disorder, called 'atypical trigeminal neuralgia', may cause less intense, constant, dull burning or aching pain, sometimes with occasional electric-shock-like stabs. Both forms of the disorder most often affect one side of the face, but some patients experience pain at different times on both sides.

Diagnosis

Severe orofacial pain suggestive of trigeminal neuralgia but with physical signs such as facial sensory or motor impairment can result from cerebrovascular disease, multiple sclerosis, infections such as HIV infection, or space-occupying lesions such as neoplasms. These must therefore be excluded (Fig. 36.1) by:

- History.
- Examination, including neurological assessment, especially of the cranial nerves.
- Investigations, including:
 - imaging by radiography, magnetic resonance imaging (MRI) and computed tomography (CT) to exclude cerebral space-occupying or demyelinating lesions
 - blood tests including erythrocyte sedimentation rate (ESR) to exclude vasculitides and serology for Lyme disease or, rarely, HIV.

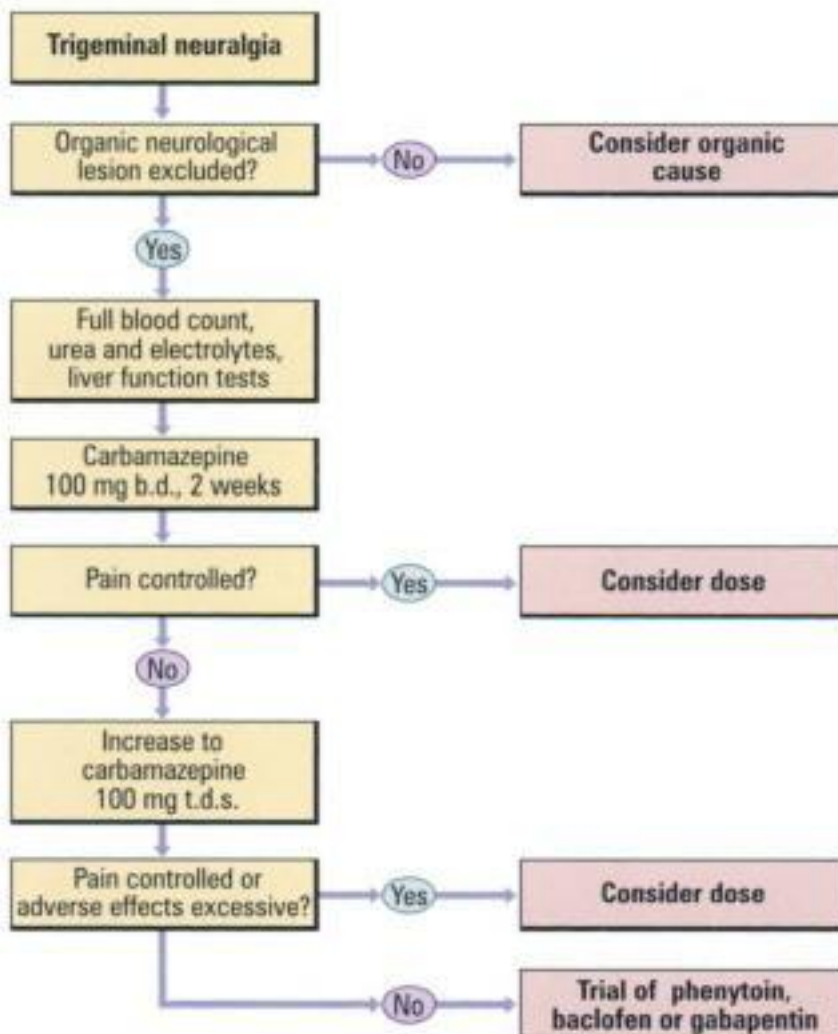


Figure 36.1 Algorithm for trigeminal neuralgia management

Management

● Patient information is an important aspect in management.

- TN is often an intermittent disease with apparent remissions for months or years, but recurrence is common and very often the pain spreads to involve a wider area over time and the intervals between episodes tend to shorten. Few patients have spontaneous remission and thus treatment is usually indicated.
- Patients with trigeminal neuralgia are best seen at an early stage by a specialist in order to confirm the diagnosis and initiate treatment.

Medical treatment

Medical treatment is used successfully for most patients, typically using anticonvulsants, especially carbamazepine, which is related to the tricyclic antidepressants. Carbamazepine:

- Is the main anticonvulsant used for control of trigeminal neuralgia.
- Prevents attacks of neuralgia in 60% of patients.
- Must be given continuously prophylactically for long periods. It is not an analgesic and, if given when an attack starts, will not relieve the pain.
- Must be used carefully and under strict medical surveillance.
- Is contraindicated in pregnancy as it is teratogenic.

Patient information sheet

TRIGEMINAL NEURALGIA

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- This is an uncommon disorder.
- The cause is unknown but involves spontaneous activity of pain nerves.
- It is not inherited.
- It is not known to be infectious.
- Similar symptoms may be seen in some neurological conditions (which we will exclude).
- There are usually no long-term consequences.
- X-rays, scans and blood tests may be required.
- Symptoms may be controlled but not cured by drugs with an anticonvulsant action.
- Uncontrolled pain may be treated by freezing the nerve, or surgery.
- Useful websites:
<http://www.painfoundation.org>
<http://www.tna-support.org>

- The dose regimen is typically to start with 100 mg twice daily for 2 weeks, then three times daily, increasing by 100 mg every 3 days to a maximum of 1000 mg/day. Most patients respond to 200–400 mg carbamazepine three times daily.
- The dose should be increased to control the pain, while at the same time avoiding ataxia and other adverse effects.
- Blood monitoring can be useful to control the dose.
- Adverse effects may be seen in up to one-third of patients and include mainly:
 - ataxia
 - drowsiness
 - visual disturbance
 - headache
 - gastrointestinal effects
 - facial dyskinesias
 - folate deficiency
 - hypertension.
- Other less common but potentially serious adverse effects include:
 - rashes, sometimes severe and exfoliative, and rarely even life-threatening
 - pancytopenia or rarely leukopenia, which is idiosyncratic and typically occurs within the first 3 months of treatment.
- Monitoring of patients should include:
 - balance (disturbed – ataxia); this tends to be the feature that limits the dose of carbamazepine
 - blood pressure (may increase); patients must have a baseline test and then blood pressure estimations for 3 months, then 6-monthly
 - blood tests – electrolytes (sodium levels may be reduced – hyponatraemia); patients must have a baseline test and then monthly tests of urea and electrolytes; liver function (may be impaired; patients must have a baseline test and then liver function tests (bilirubin, transaminases) for 3 months, then 6-monthly); bone marrow function (red and white cells and/or platelets may be depressed; patients must have a baseline and then monthly tests of red and white cell and platelet numbers, and corrected whole blood folate levels).
- May interact with cimetidine and isoniazid, potentiates lithium and interferes with oral contraceptives.

If carbamazepine fails to control trigeminal neuralgia, other choices which may be effective include:

- phenytoin
- gabapentin
- baclofen

- oxcarbazepine
- valproate
- clonazepam
- lamotrigine
- antidepressants.

Some patients report having reduced or relieved pain by means of alternative medical therapies such as acupuncture, chiropractic adjustment, self-hypnosis or meditation.

Surgical treatment

Should medication be ineffective, or if it produces excessive undesirable side-effects, neurosurgical procedures are available to relieve pressure on the nerve or to reduce nerve sensitivity. These can all also produce sensory loss as well as pain relief, and include:

- Peripheral surgery; which involves deliberately interrupting nerve conduction in a division or branch of the trigeminal nerve, and may bring temporary relief of analgesia without permanent anaesthesia. These procedures include:
 - local cryosurgery
 - injections of streptomycin or glycerol around the mandibular or infraorbital foramen
 - peripheral neurectomy of a whole division of the trigeminal nerve, using alcohol or phenol
 - radiofrequency thermocoagulation.
- Central neurosurgery; for intractable cases. This can be employed with the object either of inactivating the trigeminal nerve flow, when unfortunately the pain is exchanged for anaesthesia (and, therefore, a risk of damage to the cornea) and, sometimes, continuous anaesthesia but with pain (anaesthesia dolorosa), or to decompress the trigeminal nerve (microvascular decompression (MVD)).
- Gasserian ganglion operations:
 - injections (alcohol, glycerol or phenol) around the trigeminal ganglion (rhizolysis)
 - radiofrequency thermocoagulation ganglionolysis
 - trigeminal ganglion microcompression using a Fogarty balloon catheter.
- Posterior cranial fossa procedures; these are the most successful in providing prolonged pain relief, but morbidity and even mortality are possible:
 - trigeminal nerve decompression (MVD)
 - injections around the trigeminal nerve roots (alcohol, glycerol or phenol rhizolysis)

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- oxycodone
- carbamazepine (see above)
- topical capsaicin 0.025% or lidocaine
- transcutaneous electrical nerve stimulation (TENS).

Spontaneous improvement may follow, however, after about 18–36 months in some patients.

Websites

Trigeminal Neuralgia Association: <http://www.tna-support.org>

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PDFREE COMUNIDAD ODONTOLOGICA

Eponymous and other Conditions

This chapter includes synopses of a number of eponymous and other conditions relevant to oral medicine presented alphabetically. If a specific condition is not found here, the reader is referred to the index, since it may well be located elsewhere in the book.

Abrikossof's tumour Granular cell myoblastoma (tumour).

Acanthosis nigricans A rare paraneoplastic condition where papillomatous oral lesions are seen in patients with internal malignancy.

Achondroplasia Achondroplasia (chondrodystrophia fetalis), the most common form of short-limbed dwarfism, is usually an autosomal dominant condition in which endochondral ossification is reduced. Affected patients are dwarfs having disproportionately short limbs, bowed legs, kyphosis, prominent buttocks and abdomen, and trident hands with relatively short fingers. The skull is relatively large, having prominent frontal, occipital and parietal bones. The middle third of the face can be hypoplastic and the nasal bridge depressed. The foramen magnum is often narrow and spinal cord compression can occur at this and lower levels. Joints can be of limited mobility and the pelvic inlet narrow. Aside from the earlier mentioned facial features, achondroplasts may have a class III type malocclusion.

Acrodermatitis enteropathica A rare genetically determined disorder of zinc metabolism causing mouth ulceration and candidiasis, rash around body orifices, and alopecia.

Actinomycosis A rare bacterial infection below the mandibular angle (not lymph nodes) that may follow jaw fracture or tooth extraction. Prolonged, therapy, usually with penicillin, is indicated.

Acute ulcerative gingivitis A non-contagious anaerobic infection associated with overwhelming proliferation of *Borrelia vincentii* and fusiform

bacteria. Predisposing factors include smoking, viral respiratory infections and immune defects such as in HIV/AIDS. Uncommon, except in lower socio-economic classes, this is typically an infection of adolescents and young adults, especially in institutions, armed forces, etc.

Characteristic features include severe soreness, profuse gingival bleeding, halitosis and a bad taste. Interdental papillae are ulcerated with necrotic slough. Malaise, fever and/or cervical lymph node enlargement (unlike herpetic stomatitis) are rare. Cancrum oris (noma) is a very rare complication, usually in debilitated children.

Diagnosis is usually clinical. Smear for fusospirochaetal bacteria and leucocytes; blood picture occasionally. Occasionally there may be confusion with acute leukaemia or herpetic stomatitis. Management is by oral debridement, metronidazole (penicillin if pregnant) and oral hygiene.

Addison's disease (hypoadrenocorticism) A rare disease of young or middle-aged females. Adrenocortical destruction and subsequent increased release of pituitary adrenocorticotrophic hormone (ACTH). Causes include autoimmune hypoadrenalism (idiopathic or autoimmune) and, rarely, tuberculosis, histoplasmosis (sometimes in HIV/AIDS) and carcinomatosis. Hypoadrenocorticism leads to weight loss, weakness, hypotension and hyperpigmentation, especially in sites usually pigmented or traumatised. Brown pigmentation affects the gingiva, occlusal line and elsewhere and there may be hyperpigmentation of areolae and genitals, in flexures, and at sites of trauma. Diagnosis is from low blood pressure, low plasma electrolyte and cortisol levels and impaired response to ACTH stimulation (Synacthen test). Management is replacement therapy (fludrocortisone and corticosteroids).

Adies' (Holmes–Adie) pupil A benign condition in which one pupil is dilated and reacts only very slowly to light or convergence. There may be associated loss of knee or ankle jerks.

Albers–Schonberg disease Osteopetrosis.

Albright syndrome Albright syndrome (McCune–Albright syndrome) is polyostotic fibrous dysplasia with skin pigmentation and an endocrine abnormality (usually precocious puberty in girls).

Alstrom syndrome Congenital nerve deafness and retinitis pigmentosa.

Amalgam tattoo A black or bluish-black asymptomatic solitary small pigmented area beneath normal mucosa; usually close to the lower ridge or buccal vestibule caused by amalgam particles or dust becoming incorporated in healing wounds after tooth extraction or apicetomy or beneath mucosa. Diagnosis is from clinical features, but it may rarely be radio-opaque. It may be necessary to excise to exclude melanoma.

Amelogenesis imperfecta A rare genetic defect of enamel formation, with a wide variety of patterns. Diagnosis is from clinical features (Fig. 37.1). Fluorosis, tetracycline staining, dentinogenesis imperfecta and oculodentodigital dysplasia may need to be differentiated. Management requires restorative dental care.

Hypocalcified types Normal enamel matrix and morphology, but incomplete calcification. Enamel is opaque, white to brownish-yellow, but darkening with age. Tooth shape is normal, but the teeth are soft and chip under attrition (Fig. 37.1).

Hypoplastic types A defective matrix, but normal calcification. Enamel is hard and shiny, but malformed, often pitted and stained.

Amyloidosis The deposition in tissues of an eosinophilic hyaline material, with a fibrillar structure on ultramicroscopy. Primary (including myeloma-associated) amyloidosis is associated with deposits of immunoglobulin light chains. Manifestations include macroglossia and oral petechiae or blood-filled bullae (secondary purpura). Secondary amyloidosis is seen mainly in rheumatoid arthritis and ulcerative colitis, rarely affects the mouth, and is associated with deposits of AA proteins. Diagnosis is from biopsy; blood picture; erythrocyte sedimentation rate (ESR) and marrow biopsy; serum proteins and electrophoresis; urinalysis (Bence-Jones proteinuria); skeletal survey for myeloma. Management is by chemotherapy with melphalan, corticosteroids or fluoxymesterone.

Aneurysmal bone cyst This is not a cyst at all. It may occur in any part of the skeleton. The aetiology remains obscure: approximately one-third appear to be associated with other disorders such as a giant cell lesion, fibrous dysplasia and ossifying fibromas.

This rare lesion presents as an asymptomatic hard swelling of the jaw, sometimes following a history of previous trauma. An aneurysmal bone



Figure 37.1 Amelogenesis imperfecta

cyst usually presents as a firm, painless swelling of the mandible, which expands and subsequently perforates the cortices. Radiographs show a unilocular, or multilocular translucency with a honeycomb or soap-bubble appearance. Preoperative aspiration shows bloody fluid. A haematocrit should be performed on the aspirate, which often has a low haematocrit, differentiating it from undiluted blood in a vascular anomaly such as an haemangioma. Diagnosis is confirmed by histology which shows numerous capillaries and blood-filled spaces, areas of haemorrhage associated with multinucleated giant cells and irregular areas of osteoid. Treatment is by thorough curettage or excision.

Angina bullosa haemorrhagica (localised oral purpura) Blood blisters in the mouth or pharynx, mainly on the soft palate, seen in the absence of any immunological or platelet-associated cause. There is rapid onset, with breakdown of the blister in a day or two to an ulcer. Seen mainly in the elderly, the aetiology is unclear, though there are occasional associations with the use of steroid inhalers. Diagnosis is from clinical features, although it may be necessary to confirm haemostasis is normal; and rarely to biopsy to exclude pemphigoid. It needs to be differentiated from pemphigoid and other vesiculobullous disorders, trauma and purpura. Management is by reassurance. Topical analgesics may provide symptomatic relief.

Angiomas See haemangiomas (p. 432).

Angiomyoma A rare benign hamartoma involving blood vessels and muscle.

Ankyloglossia (tongue-tie) An uncommon condition which results in the lingual fraenum anchoring the tongue tip, restricting protrusion and lateral movements of tongue. Oral cleansing (but not speech) is impaired. There may be a genetic basis. Tongue-tie is also seen in some rare syndromes. Differentiate from tethering of tongue by scarring in epidermolysis bullosa. Management is by surgery (fraenectomy) if severe.

Antral carcinoma A rare, and usually squamous carcinoma, and the only identified predisposing factor appears to be occupational exposure to wood dust. It is seen mainly in elderly males. Initially asymptomatic, when the carcinoma invades the orbit or other structures it may cause swelling of cheek or eye area, nasal obstruction or pain. Symptoms depend on the main direction of spread.

- Oral invasion; causing pain and swelling of palate, alveolus or sulcus. Teeth may loosen.
- Ocular invasion; causing ipsilateral epiphora, diplopia or proptosis.
- Nasal invasion; causing nasal obstruction or a blood-stained discharge.

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usually becomes apparent in the third decade as a cyst. It requires excision.

PDFFREE.COMUNIDAD ODONTOLÓGICA

Bruton syndrome Sex-linked agammaglobulinaemia, cervical lymph node enlargement, oral ulceration, recurrent sinusitis, absent tonsils.

Bullous pemphigoid A blistering skin disease with crops of tense, fluid-filled blisters develop on the skin, often in body folds. Although sometimes localised to one area such as an ankle, it is usually widespread. The diagnosis is confirmed by biopsy. Bullous pemphigoid is treated with prednisolone.

Burkitt's lymphoma A lymphoma caused by Epstein-Barr virus, most common in sub-Saharan African endemic malaria areas, especially Uganda and Kenya, often affecting the jaws. Most prevalent in children, Burkitt's lymphoma is characterised by lymphomatous deposits in many tissues, especially the jaws (in 50% of patients). Burkitt's lymphoma responds well to chemotherapy.

Byar-Jurkiewicz syndrome Gingival fibromatosis, hypertrichosis, giant fibroadenomas of the breast, and kyphosis.

Cannon's disease Congenital white sponge naevus.

Carabelli's cusp Congenital additional palatal cusp on upper molars.

Carotid body tumour A slow-growing, but malignant neoplasm of chromaffin cells that both invades locally and metastasises. It presents as a mass over the internal carotid artery and transmits the carotid pulsation. It must be resected.

Castleman's disease A rare disorder characterised by benign tumours in lymph node tissue throughout the body (i.e. systemic disease (plasma cell type)).

CATCH22 CATCH22 stands for cardiac abnormality, abnormal facies, T-cell deficit due to thymic hypoplasia, cleft palate, and hypocalcaemia due to hypoparathyroidism, caused by a chromosome 22 defect.

Cat-scratch disease Infection with *Bartonella (Rochilimaea) henselae*, a Gram-negative bacterium, almost always acquired by a scratch or close contact with a cat, especially a kitten. Characterised by indolent, sometimes suppurative, regional lymphadenitis. Most cases are children who develop a primary 'tender' non-pruritic papule after 3–10 days and then unilateral regional lymphadenitis, sometimes with mild fever and malaise. Diagnosis is from history together with culture and occasionally biopsy. There is often a mild leucocytosis and raised erythrocyte sedimentation rate (or plasma viscosity). The disease is typically self-limiting, but antimicrobials (erythromycin or doxycycline) may be indicated.

Chediak–Higashi syndrome A congenital immune defect in which neutrophils have large inclusions.

Cheek biting (morsicatio buccarum) Common and seen in adults mainly, especially anxious patients, and those with other psychologically related disorders, e.g. temporomandibular pain–dysfunction syndrome, it is also rarely caused by self-mutilation, seen in psychiatric disorders, learning disability and some rare syndromes with insensitivity to pain. Abrasion of the superficial epithelium leaves whitish fragments on reddish background. The lesions are invariably restricted to the lower labial mucosa and/or buccal mucosa near the occlusal line on one or both sides.

Chemical burns Can be caused by various chemicals or drugs; notably aspirin put in the sulcus to try to relieve toothache. A white lesion with sloughing mucosa localised usually to the buccal sulcus and adjacent buccal mucosa is seen, often alongside a carious tooth. Diagnosis is by history and clinical features.

Cherubism A genetically determined disease of the jaws which in many ways closely resembles fibrous dysplasia except that there is an autosomal dominant mode of inheritance (but variable expression) and it presents at 2–4 years of age. The lesions grow progressively until puberty when they usually arrest or regress. Painless symmetrical enlargement at the angles of the mandible and in the maxilla leads to the typical ‘cherubic’ facial appearance. Expansion of the alveolar bone results in irregular spacing and premature loss of teeth and possibly disturbances to a developing dentition. Radiography shows well-defined multilocular radiolucencies in the mandible, but maxillary lesions are less clearly defined. Blood chemistry is essentially normal, although there may be a raised alkaline phosphatase during periods of most active growth. Histologically, the lesions consist of loose vascular connective tissue with numerous multinucleated giant cells and, as in fibrous dysplasia, there is replacement of bone by the fibrous tissue. However, metaplastic bone formation is an infrequent finding. Other fibro-osseous lesions and giant cell lesions of bone (giant cell granuloma, hyperparathyroidism, giant cell tumours) should be excluded. Treatment of cherubism is as for fibrous dysplasia (see also Noonan syndrome, p. 448).

Chondroectodermal dysplasia (Ellis–van Creveld syndrome) Autosomal-recessive polydactyly and chondrodysplasia.

Chondroma A benign tumour, rare in the jaws. The anterior maxilla, mandibular symphysis and the coronoid and condylar processes are the most common sites. Chondromas are typically found in the elderly and

form slow-growing, painless masses. Provided surgical excision of these masses is complete, then recurrence is unlikely.

Chondrosarcomas These tend to affect the elderly and, although isolated cases arise from chondromas, most arise *de novo*. The behaviour is very unpredictable, but many grow rapidly and produce extensive local destruction. Radical surgery, the only means of eradicating the tumour, can be difficult as the edges may not be apparent clinically or radiographically. Multiple local recurrence is common and the prognosis is worse than for osteosarcoma.

Chorea Consists of a writhing movement of continuous abrupt and intermittent movements that flow randomly from one part of the body to another. Chorea may affect the head and neck especially in tardive dyskinesia. This is usually a late (hence tardive) complication manifesting as non-random, focal patterned or stereotyped movement induced by dopamine receptor blocking drugs such as metoclopramide, phenothiazines or butyrophenones and is somewhat similar to oromandibular dystonia. Senile chorea, including edentulous dyskinesia or orodyskinesia, is found in 16% of the edentulous.

Christmas disease A deficiency of blood clotting factor IX.

Chronic ulcerative stomatitis This consists of chronic oral lesions similar to erosive lichen planus, with ulcers and erosions affecting mainly the buccal or lingual mucosae, but sometimes the gingivae. The lesions and clinically normal mucosa have a distinct pattern of a particulate stratified squamous-epithelium-specific (SES) antinuclear antibody (ANA) on direct immunofluorescent examination of perilesional tissue, and patients can have circulating ANA. Biopsy of perilesional tissue, with histological and immunostaining examination are essential to the diagnosis.

Hydroxychloroquine is effective therapy.

Chvostek's sign Tapping the skin over the facial nerve elicits involuntary twitching of the muscles of the upper lip or ipsilateral side of face – a sign of hypocalcaemia, typically from hypoparathyroidism.

Cleidocranial dysplasia (dysostosis) A rare autosomal dominant condition, or mutation. Clinical features include exaggerated transverse diameter of cranium, delayed fontanelle closure, multiple wormian bones, frontal and parietal bossing, depressed nasal bridge, maxillary hypoplasia, underdeveloped paranasal sinuses, high arched palate (? cleft), delayed or failed tooth eruption, multiple supernumerary teeth, dentigerous cysts, aplastic or hypoplastic clavicles (shoulders can be approximated), short stature and other skeletal anomalies.

Diagnosis is from the family history and ability to bring together the shoulders, jaw, skull and skeletal radiography.

Management is to leave unerupted teeth untreated unless there are complications. Eruption of permanent teeth is retarded and dentigerous cysts are frequently found. Supernumerary teeth are common in cleidocranial dysplasia, especially in the anterior mandible. The crowns of the teeth are normal, but the roots can be short, thin and lack acellular cement. Surgery is often necessary.

Cockayne syndrome Premature ageing, dwarfism, deafness and neuropathy.

Coffin–Lawry syndrome Congenital osteocartilaginous anomalies and learning disability.

Coffin–Siris syndrome Congenital defective neutrophil function, susceptibility to infection, and skin pigmentation.

Congenital epulis A rare reactive process seen on the alveolus of a neonate.

Constricted pupils Constricted pupils (miosis) can be caused by sympathetic nerve lesions, cholinergic drugs (e.g. pilocarpine or neostigmine) or opiates (heroin, etc.). Thus heroin addicts may be recognised by 'pin-point pupils'. Raised intracranial pressure is the most important cause of pupil constriction and is noted when the pupil also becomes non-reactive owing to pressure on the oculomotor nerve. It may occur after head injury, intracranial haemorrhage or brain tumour.

Costen syndrome An outmoded term relating to patients with facial pain, otalgia and possible occlusal abnormalities, replaced by the term 'temporo-mandibular pain–dysfunction syndrome'.

Cowden syndrome Congenital multiple hamartoma syndrome, with oral papillomatosis and risk of breast and thyroid cancer.

Coxsackie virus Named not after a person, but a place in New York state, there are a number of Coxsackie viruses, and they can cause herpangina, hand, foot and mouth disease, and other illnesses.

Cranial arteritis Cranial arteritis (temporal arteritis; giant-cell arteritis) is a febrile, often self-limiting disease which affects old people and is characterised by painful inflammation of the superficial temporal and other cranial arteries, malaise, weakness, weight loss, anorexia, fever, sweating and a raised erythrocyte sedimentation rate (ESR) (or plasma viscosity). The headache is intense, deep and aching, throbbing in nature and persistent, frequently made worse when the patient lies flat in bed and may be exac-

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Di George syndrome Congenital immunodeficiency with cardiac defects and thyroid defects and hypoparathyroidism due to a third branchial arch defect related to a chromosome 22 anomaly (CATCH22 syndrome).

Dilated pupils Dilated pupils (mydriasis) can be caused by parasympathetic lesions affecting the third nerve, Holmes-Adie syndrome, Horner syndrome, anticholinergic drugs (e.g. atropine or similar drugs), sympathomimetic drugs (e.g. adrenaline, cocaine). Users of cocaine or crack cocaine may thus have dilated pupils.

Down syndrome Down syndrome (trisomy 21) is the commonest recognisable congenital chromosomal anomaly. Patients have learning disability and are of short stature with a characteristic appearance of brachycephaly, midface retrusion, and upward sloping palpebral fissures (Mongoloid slant). Dental anomalies are common.

Duhring's disease Dermatitis herpetiformis.

Dysarthria Disordered speech. Normal speech involves a complex series of muscles, particularly the muscles of respiration, larynx, pharynx, palate, tongue and lips and, like all voluntary muscle activity is under control from higher centres, both pyramidal and extrapyramidal. The act of speaking is a highly coordinated sequence involving articulation and phonation under direct control of the vagus, glossopharyngeal, hypoglossal and facial nerves. Conditions affecting the tongue, palate, pharynx, larynx or these nerves or their central connections can lead to disturbed speech. However, speech also involves a wide range of acquired skills, deficiencies of which impede interpersonal communication irrespective of any other impairment in language usage.

Deranged speech can be due commonly to drugs (including alcohol), CNS disorders as in learning disabilities, delirium or dementia, loss of voice due to laryngeal disease or paralysis (dysphonia), or defects in articulation because of paralysis, rigidity, or involuntary movements of tongue or palate. The most common oral cause of dysarthria is immobility of the tongue after a lingual block local analgesic injection, trauma to the tongue, scarring, diseases affecting the tongue (such as carcinoma) or foreign bodies (such as in oral piercing). Spastic dysarthria is usually caused by cerebrovascular disease affecting the motor cortex (causing pseudobulbar palsy), extrapyramidal disease such as Parkinsonism or drugs such as phenothiazines; basal ganglia disease causes choreic dysarthria; cerebellar disease causes ataxic dysarthria. Alcohol also has this effect. Paralytic dysarthria is less common, but may be caused by medulla oblongata disease (bulbar palsy), cranial nerve lesions affecting nerves VII, IX, X, XI or XII, myopathies such as myasthenia gravis. Patients with persistent dysarthria should be referred for a neurological opinion.

Dyskinesias Abnormal movements of the tongue or facial muscles, sometimes with abnormal jaw movements, bruxism or dysphagia. Involuntary tongue protrusion and retraction, and facial grimacing are common dyskinesias. They differ from dystonias mainly in that muscle spasm is less prominent, but they may be difficult to differentiate clinically. They are usually caused by extrapyramidal disease, such as athetosis, or drugs (e.g. phenothiazines, tricyclics, oral contraceptive, metoclopramide, antipsychotics). Most dyskinesias resolve within 4 weeks of stopping any causal medication. If not, treat with anti-parkinsonian drugs (e.g. benzhexol), baclofen, benzodiazepines, dopamine depletors (reserpine or tetrabenazine), calcium channel blockers, clozapine, buspirone, α -adrenergic agonists, vitamin E or botulinum toxoid.

Dysphasias Disturbances of language use (or aphasias), and may be caused by brain disease such as stroke or after head injury, in which there is loss of production and comprehension of speech and language.

Dystonias A group of uncommon diseases characterised by abnormal movements such as sustained and patterned contractions producing abnormal postures, repetitive twisting or squeezing.

Eagle syndrome This is an elongated styloid process associated with dysphagia and pain on chewing, and on turning the head towards the affected side.

ECHO viruses Enteric cytopathogenic human orphan viruses.

Ehlers–Danlos syndrome A group of congenital collagen disorders characterised by joint hyperflexibility, hyperextensible skin and bleeding and bruising, and sometimes mitral incompetence. Patients can bend the thumb right back and may be able to touch the tip of their nose with their tongue. Recurrent dislocation of the temporomandibular joint may be seen. In type VIII there is severe early onset periodontal disease with loss of permanent teeth. Dental anomalies include deep fissured premolars and molars, dentinal abnormalities such as shortened deformed roots, and multiple large pulp stones.

Ellis–van Creveld syndrome Also known as 'chondroectodermal dysplasia'. This syndrome consists of congenital polydactyly, dwarfism, ectodermal dysplasia, hypodontia and hypoplastic teeth and multiple fraenae.

Epidermolysis bullosa A rare genetically-determined disorder related to a defect in the epidermolysis bullosa antigen in the epithelial basal lamina, leading to blistering after trauma, and scarring, which may cause severe disability such as limb deformities, microstomia, ankyloglossia and trismus. Enamel hypoplasia may be seen. Diagnosis is from the family history

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Fibro-osseous lesions A group of disorders of unknown aetiology, composed of fibrous and ossified tissue. The main disorders include Paget's disease of bone, fibrous dysplasia and cherubism and the ossifying fibroma.

Fibrous dysplasia A disorder characterised by the replacement of an area of bone with fibrous tissue. The process typically starts in childhood and, as the skeleton matures, the lesions progressively ossify. As skeletal growth ceases, the lesion stabilises. Three types of fibrous dysplasia are recognised:

- *Monostotic*, in which there is a single lesion in only one bone.
- *Polyostotic*, in which several lesions are present in one or more bones.
- *Albright syndrome*, where polyostotic fibrous dysplasia is associated with cutaneous pigmentation (cafe-au-lait type) on the same side as the bony lesion, precocious puberty and, rarely, overactivity of other endocrine glands such as the thyroid, adrenal cortex or pituitary.

Fibrous dysplasia usually presents as a painless bony hard swelling. The maxillary sinus is often involved, when there may be encroachment on the orbit (causing proptosis) and nasal cavity (causing obstruction). Expansion of the alveolar bone leads to disruption of occlusion, displacement of teeth and possibly failure of eruption of teeth.

Radiographically, there is either a translucent cystic appearance in the affected bone, or mottled opaque areas likened to ground glass. The lesions are often ill-defined and may extend to, but not cross, suture lines. Serum calcium and phosphate levels are normal but, in many, the serum alkaline phosphatase level is high and urinary hydroxyproline is increased (findings similar to those in Paget's disease). Microscopically, the lesion consists of fibrous tissue that replaces the normal bone and gives rise to osseous trabeculae by metaplasia. The osseous tissue is composed of irregular ('Chinese characters') trabeculae of woven bone lined by osteoblasts. Focal degeneration of fibrous tissue accounts for the cystic spaces seen macroscopically. The treatment of choice to correct any cosmetic defect is conservative surgery, preferably after the cessation of normal skeletal growth. The lesion is not radio-sensitive; irradiation may cause sarcomatous change.

Fibrous lump or nodule Fibrous lump or nodule ('fibroepithelial polyp') is a pedunculated or broadly sessile, sometimes ulcerated, hard or soft, lump seen mainly on the buccal mucosa. It is termed 'epulis' if on the gingival margin. It is common and is probably caused by chronic irritation causing fibrous hyperplasia. Excision biopsy helps differentiate it from any other soft tissue tumour.

Fissured (plicated or scrotal) tongue An extremely common genetic condition; the dorsum has deep irregular fissures, but is normally papillated (Fig. 37.3). A fissured tongue may also be seen in Down syndrome or Melkersson–Rosenthal syndrome. There are associations with erythema migrans in particular. The diagnosis is usually clear cut. The lobulated tongue of Sjögren syndrome must be differentiated.



Figure 37.3 Fissured tongue

Fitzgerald–Gardner syndrome Gardner syndrome.

Fluorosis The condition of enamel defects caused by high levels of fluoride. High levels in drinking water are uncommon in the developed world, but are particularly common in parts of the Middle East, India and Africa. Fluorosis affects many teeth.

- *Mildest form:* white flecks or spotting or diffuse cloudiness.
- *More severe form:* yellow-brown or darker patches.
- *Most severe form:* yellow-brown or darker patches, sometimes with pitting (Fig. 37.4).



Figure 37.4 Severe fluorosis

Diagnosis is from history, clinical appearance and data about fluoride content of drinking water. It is necessary to differentiate from amelogenesis imperfecta and tetracycline staining. Management of severe forms is by the use of veneers or crowns.

Foliate papillitis The foliate papillae are found on the posterolateral border of the tongue, at the junction of the anterior two-thirds with the posterior third. The size and shape of the foliate papillae are variable and occasionally they swell if irritated mechanically or if there is an upper respiratory infection, and this is termed 'foliate papillitis'. Located at a site of high predilection for lingual cancer, they may give rise to unnecessary concern about cancer.

Fordyce disease Fordyce disease (Fordyce spots) are congenital ectopic sebaceous glands seen mainly in the buccal mucosa or lips.

Frey syndrome This is gustatory sweating and flushing of skin after trauma to skin overlying a salivary gland due to crossover of sympathetic and parasympathetic innervation to the gland and skin.

Froehlich syndrome Congenital obesity, hypogonadism, and risk of learning disability and open bite.

Furred tongue Coating of the tongue is quite commonly seen in healthy adults, particularly in edentulous patients, those who are on a soft, non-abrasive diet, those with poor oral hygiene, or those who are fasting. The coating in these instances appears to be of epithelial, food and microbial debris which collects since it is not mechanically removed. Indeed, the tongue is the main reservoir of some microorganisms such as *Candida albicans* and some *Streptococci*. The tongue may be coated with off-white debris in many illnesses, particularly febrile diseases, xerostomia and ill patients, especially those with poor oral hygiene or who are dehydrated. The history is important to exclude a congenital or hereditary cause of a white lesion. The clinical appearances may strongly suggest the diagnosis, but investigations are often required if the white lesion does not scrape away from the mucosa with a gauze. Biopsy may then rarely be indicated. Treatment is of the underlying cause.

Gardner syndrome Autosomal dominant syndrome of intestinal polyposis, bony abnormalities, and soft tissue tumours, multiple osteomas and fibromas, and pigmented lesions of the fundus of the eye.

Garré's osteomyelitis This is proliferative periostitis.

Gasserian ganglion This is the trigeminal ganglion.

Giant cell granuloma The central giant cell granuloma is an uncommon lesion only seen in the tooth-bearing regions of the jaws, most commonly

in the mandible and typically in the second and third decades. The true nature of these lesions is unknown but, as they are invariably destructive, the term 'reparative' giant cell granuloma would appear to be inappropriate. Lesions may be symptomless or simulate a malignant neoplasm clinically and radiographically. Occasionally, the lesion erodes through the cortical bone where it presents as a domed, purplish submucosal swelling. Radiography shows an ill-defined area of radiolucency and there may be resorption of the roots of related teeth. Microscopy shows multinucleated giant cells irregularly distributed in a cellular stroma of plump, spindle-shaped cells which is often highly vascular. There may be areas of new and old haemorrhage with haemosiderin pigment deposition. These microscopic features are indistinguishable from the focal lesions of hyperparathyroidism, which can only be excluded by the appropriate serological tests (calcium and phosphate levels and alkaline phosphatase). Although central giant cell granulomas may recur following curettage, they virtually never metastasise.

Gilles de la Tourette syndrome Coprolalia (utterance of obscenities).

Glossitis The term given when the tongue is sore or, more appropriately, when the dorsum of tongue becomes depapillated and red. There are several causes, including anaemia, vitamin or iron (haematinic) deficiency, chemotherapy or radiation therapy, or infection, such as candidiasis. This section discusses glossitis in haematinic deficiency states, which is seen mainly in:

- malabsorption states
- pernicious anaemia
- chronic bleeding from the gastrointestinal or genitourinary tract
- vegans
- dietary faddists
- poor socio-economic circumstances (deficiencies of vitamins of the B group other than B₁₂ are an occasional cause of glossitis, mainly seen in chronic alcoholics or in those with malabsorption).

The tongue may appear completely normal or there may be:

- Linear or patchy red lesions: especially in vitamin B₁₂ deficiency.
- Depapillation with erythema: in deficiencies of iron, folic acid or B vitamins lingual depapillation begins at the tip and margins of the dorsum, but later involves the whole dorsum (bald tongue).

Various other patterns are described, in deficiencies of:

- Riboflavin: papillae enlarge initially, but are later lost.
- Niacin: red, swollen, enlarged 'beefy' tongue.
- Pyridoxine: swollen, purplish tongue.

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Graves disease Hyperthyroidism with ophthalmopathy and exophthalmos.

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Grisman syndrome Lichen planus, diabetes and hypertension (probably actually due to lichenoid reactions to antihypertensive and antidiabetic drugs).

Guillain-Barré syndrome Acute infective polyneuritis; facial palsy may be seen.

Haemangiomas Vascular malformations that are red, purple or blue, painless, soft and sometimes fluctuant lesions that usually blanch on pressure. Most appear in infancy, but about 15% develop in later years. Haemangiomas are common on the tongue, vermilion of lip, or buccal mucosa (Fig. 37.5). Diagnosis may be assisted by aspiration, radiography, angiography, magnetic resonance imaging (MRI), and MRI-angiography. Haemangiomas may need to be differentiated from telangiectasia, purpura, Kaposi sarcoma and epithelioid angiomatosis. Management may be active, with removal of the haemangioma, or simple observation (since some 50% regress spontaneously in childhood). Cryosurgery or laser (Nd-YAG, carbon dioxide, pulsed tuneable dye or copper vapour) are the main treatments. Alternatively sclerosant injection (boiling water, absolute alcohol, sodium tetradecyl sulphate, sodium morrhuate or ethanalamine oleate), compression sutures (Popescu) or (rarely) arterial embolisation can be used.



Figure 37.5 Haemangioma in the lip

Haemangiopericytoma A rare tumour arising from pericytes; there are benign and malignant forms.

Haemochromatosis An inborn error of iron overload which may cause diabetes, cardiomyopathy, and mucocutaneous brown pigmentation or salivary swelling

Haemophilia This usually refers to haemophilia A – deficiency of blood clotting factor VIII.

Hailey–Hailey disease Autosomal-dominant, benign familial pemphigus presenting in the second or third decade with skin and oral blisters and vegetations.

Hairy leucoplakia HIV-infected and other severely immunocompromised patients may develop white oral lesions with a corrugated or 'hairy' surface ('hairy leucoplakia') which usually affects the lateral margins or dorsum of tongue. Epstein–Barr virus may be found in this lesion.

Hajdu–Cheney syndrome A rare connective tissue disorder. The most distinctive feature is ulcerating lesions on the palms and soles, accompanied by softening and destruction of bones (acro-osteolysis). Abnormal development of bones, joints and teeth also occurs.

Hallerman–Streiff syndrome Congenital cranial anomalies, microphthalmia, cataracts, mandibular hypoplasia and abnormal temporomandibular joint.

Hand, foot and mouth disease A Coxsackie virus infection (usually A16; rarely A5 or A10), which has an incubation period of 2–6 days. Clinical features include oral ulcers resembling herpetic stomatitis but affecting labial and buccal mucosa, no gingivitis, mild fever, malaise, anorexia, rash (red papules that evolve to superficial vesicles in a few days, found mainly on palms and soles). A common infection, it usually occurs in small epidemics, in children.

Diagnosis is from the clinical features. Serology is confirmatory, but rarely required. The main differentiation is from herpetic stomatitis, chickenpox. Management is symptomatic (see herpes simplex, Ch. 29).

Hand–Schüller–Christian disease Langerhans histiocytosis causing skull lesions, exophthalmos and diabetes insipidus.

Heck's disease Heck's disease (focal epithelial hyperplasia) is caused by human papilloma viruses 13 or 32, and is seen especially in ethnic groups such as American Indians and Inuits.

Heefordt syndrome Sarcoidosis associated with lacrimal and salivary swelling, uveitis and fever (uveoparotid fever).

Hemifacial spasm A spasm of the angle of the mouth or the eyelid, worse towards evening. Usually idiopathic, it may be caused by a vascular anomaly affecting the vertebrobasilar vessels (dolichoectasia) causing pressure on the VII nerve. Some cases herald a cerebellopontine angle lesion or other lesion irritating the facial nerve. Computed tomography or magnetic

resonance imaging are indicated. Local injections of botulinum toxin into the affected muscles may give relief. Anticholinergics, phenytoin, carbamazepine or benzodiazepines may help. Rarely are myectomy or microvascular decompression indicated. Hemimasticatory spasm is similar, but affects the masticatory muscles and may be associated with progressive hemifacial atrophy. It often responds to botulinum toxin.

Henoch–Schonlein purpura Allergic purpura, which may cause oral petechiae.

Hermansky–Pudlak syndrome Congenital albinism and bleeding tendency.

Herpangina An infection with a Cocksackie virus (A7, A9, A16; B1, B2, B3, B4 or B5) or echovirus (9 or 17). It has an incubation period of 2–6 days. Clinical features include oropharyngeal ulcers, no gingivitis, cervical lymphadenitis (moderate), fever, malaise, irritability, anorexia, vomiting, but no rash. Diagnosis is from clinical features. Serology (theoretically) is confirmatory. Differentiation is from herpetic stomatitis and chickenpox. Management is symptomatic.

Hodgkin's disease Lymphoma which can affect any age group, particularly males in middle age. There is progressive involvement of lymphoid tissue, often beginning in the neck. The lymph nodes become enlarged, discrete and rubbery. Pain, fever, night sweats, weight loss, malaise, bone pain and pruritus are common. Drinking alcohol may cause pain in affected lymph nodes. Treatment by chemotherapy and radiotherapy is now remarkably successful.

Holoprosencephaly A common developmental defect affecting the neural crest cells populating the frontonasal mass and the forebrain with the associated appearance of midface defects.

Horner syndrome This comprises, usually, unilateral:

- miosis (pupil constriction)
- ptosis (drooping of the upper eyelid)
- loss of sweating of the ipsilateral face
- apparent enophthalmos (retruded eyeball).

It is caused by interruption of sympathetic nerve fibres peripherally as a result, for example, of trauma to the neck, or lung cancer infiltrating the superior cervical sympathetic ganglion.

Horton's cephalgia Migrainous neuralgia.

Human papilloma viruses DNA epitheliotropic viruses which most commonly produce papillomas, but are also implicated in skin warts and venereal warts (condyloma acuminatum), and rare disorders, e.g. focal epithelial

hyperplasia (Heck's disease). A higher prevalence is seen in patients with ~~sexually transmitted diseases~~ or who are immunocompromised as in HIV/AIDS.

- Papillomas are uncommon in the mouth but typically seen on the fauces, soft palate or tongue, usually less than 5 mm diameter and with whitish filiform projections.
- Warts are rare in the mouth:
 - verrucae vulgaris, usually transmitted from skin lesions, are found predominantly on the lips
 - condyloma acuminata transmitted from genital or anal lesions, are found mainly on the tongue or palate.

Diagnosis is by biopsy to differentiate from other tumours. Management is by use of podophyllum or by imiquimod, excision, or laser, electro- or cryosurgery.

Hunterian chancre Syphilitic primary chancre.

Hurler syndrome Congenital mucopolysaccharidosis causing growth failure, learning disability, large head, frontal bossing, hypertelorism, coarse facial features (gargoylism) and mandibular radiolucencies.

Hutchinson–Gilford syndrome Progeria (see Werner syndrome, p. 474).

Hutchinson's teeth Screwdriver-shaped incisor teeth in congenital syphilis.

Hutchinson's triad Hutchinson's teeth, interstitial keratitis and deafness.

Hyperparathyroidism

Primary hyperparathyroidism Primary hyperparathyroidism is usually due to a parathyroid adenoma, carcinoma or hyperplasia of parathyroid tissue or ectopic production of parathyroid hormone (PTH) (e.g. by tumours of lung or kidney). May also rarely occur in association with adenomas of other endocrine glands (the multiple endocrine adenoma syndromes). Serum calcium levels are raised, as usually is the alkaline phosphatase. Phosphate levels are reduced. The clinical features are the direct result of either excess PTH or calcium, and particularly include renal stones, bone lesions, polyuria and abdominal pain ('stones, bones and abdominal groans'). Anorexia and psychoses are not uncommon.

Secondary hyperparathyroidism Secondary hyperparathyroidism is usually the consequence of renal disease in which low serum calcium as a consequence of impaired renal production of dihydroxycholecalciferol induces increased parathyroid activity, and eventually hyperplasia of the parathyroid glands. Secondary hyperparathyroidism may also follow malabsorption syndromes. Calcium levels are usually normal or low.

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Jackson–Lawler syndrome A type of pachyonychia congenita with no oral leukoplakia, but neonatal teeth and early loss of secondary teeth.

Jadarsohn–Lewandowski syndrome This is pachyonychia congenita.

Jones syndrome Curry–Jones syndrome.

Kaposi sarcoma A malignant neoplasm of endothelial cells caused by human herpesvirus 8. It is virtually unknown in the mouth except in HIV/AIDS or immunosuppressed organ transplant patients. Occasionally, in elderly Jews and those of Mediterranean or Middle Eastern origin, Kaposi sarcoma appears in the absence of an identified immune defect. Usually oral lesions are part of more widespread disease but, in AIDS, Kaposi sarcoma early lesions are red, purple or brown macules. Later these become nodular, extend, and may ulcerate and disseminate. Kaposi sarcoma typically involves the palate or gingivae. Diagnosis is confirmed by biopsy. Other pigmented lesions, especially epithelioid angiomatosis, haemangiomas, lymphomas and purpura may need to be differentiated. Management is by treatment of the underlying predisposing condition if possible; and then radiotherapy or vinca alkaloids systemically or intralesionally.

Kartagener's syndrome Congenital dextrocardia, immunodeficiency and sinusitis.

Kawasaki disease Kawasaki disease (mucocutaneous lymph node syndrome) is an idiopathic disorder with fever, lymphadenopathy, desquamation of hands and feet, cheilitis and cardiac lesions.

Kikuchi–Fujimoto disease A self-limited lymphadenopathy that can be confused histologically and clinically with lymphoma or systemic lupus erythematosus.

Kimura's disease A chronic inflammatory condition that presents with a characteristic triad of signs and symptoms of a painless, slowly enlarging soft tissue mass (or masses), associated lymphadenopathy and peripheral eosinophilia. Eighty-five per cent of cases occur in males.

Klinefelter syndrome A chromosome abnormality that affects only men and causes hypogonadism.

Klippel–Feil anomaly Congenital association of cervical vertebrae fusion and short neck, low-lying posterior hairline, syringomyelia and other neurological anomalies, and sometimes unilateral renal agenesis and cardiac anomalies.

Koplik's spots Small white spots on the buccal mucosa seen during the measles prodrome.

Kveim test An outdated skin test for sarcoidosis. An intradermal test in which an antigen prepared from the lymph nodes or spleen of human sarcoidosis patients was injected intracutaneously, and positive when an infiltrated area, papule, nodule or superficial necrosis appeared around the site of injection or a skin biopsy yielded typical tubercles and giant cell formations upon histological examination.

Laband syndrome Laband syndrome (Zimmerman–Laband syndrome) is a form of hereditary gingival fibromatosis with skeletal anomalies and large digits.

Langerhans cell histiocytoses Langerhans cell histiocytoses (histiocytosis X) is a group of rare neoplasm arising from Langerhans cells (dendritic intraepithelial macrophage-like cells). Swelling and gingival ulceration, particularly in the molar region, are common manifestations and the teeth may loosen and exfoliate. Failure of healing of a socket, or the appearance of a pathological fracture may be the presenting feature. The spectrum includes:

- Solitary eosinophilic granuloma of bone: usually benign with osteolytic lesion only and seen in adults. There is sometimes gross periodontal destruction.
- Multifocal eosinophilic granuloma: Hand–Schuller–Christian disease, a more malignant form in children and young adults characterised by osteolytic lesions and sometimes diabetes insipidus and proptosis.
- Letterer–Siwe disease: the most malignant form; seen in infants and characterised by failure to thrive, fever, hepatosplenomegaly and skeletal osteolytic lesions that may cause pain, swelling and loosening of teeth.

Radiography is indicated. Differentiate from other osteolytic disorders, especially carcinomatosis and myelomatosis. Diagnosis is by biopsy: foamy macrophages (Birbeck granules may be seen by EM), eosinophils and bone destruction. Surgery is used to manage solitary lesions; radiotherapy/chemotherapy for multifocal disease.

Larsen syndrome A mainly autosomal recessive condition, consisting of cleft palate, flattened facies, multiple congenital dislocations and deformities of the feet.

Laurence–Moon–Biedl syndrome Congenital retinitis pigmentosa, obesity, polydactyly, learning disability and blindness.

Leiomyoma A rare benign tumour from smooth muscle.

Lesch–Nyhan syndrome Congenital defect of purine metabolism causing learning disability, choreoathetoid cerebral palsy and aggressive self-mutilation.

Letterer-Siwe disease Rapidly progressive disseminated form of **Langerhans histiocytosis** which can be fatal because of pancytopenia and multisystem disease.

Leukaemia A malignant proliferation of leucocytes. Common oral manifestations in leukaemia include lymphadenopathy, bleeding, petechiae, gingival swelling, ulceration. Other findings include sensory changes (particularly of the lower lip), extrusion of teeth, painful swellings over the mandible, parotid swelling (Mikulicz syndrome), fungal infections, and predisposition to herpes virus lesions. Diagnosis is confirmed by a blood film, white cell count (raised), differential count (shows blasts), platelet count (reduced) and bone marrow biopsy. Treatment is mainly by chemotherapy. Oral hygiene should be carefully maintained with chlorhexidine mouth rinses and the use of a soft toothbrush.

Prophylactic antifungal and antiviral therapy (nystatin or amphotericin) is also indicated (see Ch. 29). Many of the chemotherapeutic agents can cause oral ulceration. Methotrexate is a major offender, but ulceration may be prevented or ameliorated by concomitant intravenous administration of folinic acid ('leucovorin rescue') or topical folinic acid. There are several types of leukaemia.

Acute lymphoblastic leukaemia (ALL) The most common leukaemia of childhood, it has a peak incidence at 3–5 years of age. Malignant lymphoblasts proliferate and infiltrate the viscera, skin and central nervous system. Marrow infiltration causes granulocytopenia (predisposing to infections), thrombocytopenia (causing a bleeding tendency) and anaemia ('there is no leukaemia without anaemia').

Acute myeloblastic leukaemia (AML) The most common acute leukaemia of adults. Features are similar to acute lymphoblastic leukaemia, but central nervous system involvement is rare.

Chronic lymphocytic leukaemia (CLL) The most common chronic leukaemia. It mainly affects the elderly. Some patients are asymptomatic, while in others there is fever, weight loss, anorexia, haemorrhage and infections. Lymph node enlargement is early and may be detected in the neck. CLL may need no treatment.

Chronic myeloid leukaemia (CML) This is characterised by proliferation of myeloid cells in the bone marrow, peripheral blood and other tissues, and mainly affects those over 40 years of age. Splenomegaly and hepatomegaly are common. Anaemia, weight loss and joint pains are not uncommon. The prognosis is variable, but sooner or later there is transformation to an acute phase similar to AML (blast crisis).

Leucoedema Leucoedema is not a mucosal disease, but simply the description of very faint whitish lines in some normal buccal mucosae,

seen very often in people of African origins. The whitish lines disappear if the mucosa is stretched (a diagnostic test).

Leucopenia This may result from viral infections (especially HIV infection), drugs, irradiation, or can be idiopathic. There is a predisposition to infections and ulcers, characteristically persistent ulcers lacking an inflammatory halo. Diagnosis is confirmed by a full blood picture and a bone marrow biopsy, if appropriate. Management is by improving oral hygiene; antimicrobials as necessary.

Lewar's disease Lewar's disease (pulse granuloma) is a variety of periostitis and osteitis. The typical presentation is of an edentulous patient with a bony hard subperiosteal mass in the lower buccal sulcus indented or ulcerated by a denture flange. Hyaline bodies seen on histology seem to be vegetable leguminous pulses, which have provoked a foreign body reaction. It has been proposed that vegetable matter becomes embedded under the mucosa following tooth extraction or by pressure from the denture. Treatment is by curettage.

Linea alba (occlusal line) A simple line of frictional keratosis seen in the buccal mucosae, horizontally aligned with the occlusal surfaces of the teeth, sometimes with small vertical lines coincident with the interdental areas. More prominent where there is bruxism or clenching. No treatment is required. The tongue is often scalloped also.

Linear IgA disease and chronic bullous dermatosis of childhood These are subepithelial immune blistering diseases in which there is linear deposition of IgA autoantibodies at the epithelial basement membrane zone. These result in adults in linear IgA disease (LAD) and in children in chronic bullous disease of childhood.

- *Linear IgA disease* presents with oral lesions that mimic those of mucous membrane pemphigus, in particular oral vesicles and ulcers.
- *Chronic bullous dermatosis* of childhood presents with similar oral lesions and there can sometimes be scarring.

Diagnosis is by biopsy of perilesional tissue, with histological and immunostaining. Most patients respond to high-dose prednisolone, dapsone or sulphonamides.

Lipoma A rare benign tumour of adipose tissue, presenting as a slow-growing, yellowish, soft, semifluctuant, painless mass usually in the buccal mucosa. Diagnosis is by biopsy; management is by excision.

'Loose bodies' Hydroxyapatite crystal deposits within the temporomandibular joint space. They may be seen in osteochondritis dissecans (1–3 'loose bodies'); osteoarthritis (1–10 'loose bodies'); chip fracture

of the articular surface (1–3 'loose bodies'); or synovial chondromatosis (50–500 'loose bodies'); and can cause pain. If the pain does not respond to conservative treatment, surgical exploration of the joint may be needed.

Lowe syndrome Lowe syndrome (cerebrohepatorenal syndrome) is congenital hypotonia and flexion contractures.

Ludwig's angina Infection of sublingual and submandibular fascial spaces.

Lupus erythematosus A rare autoimmune disease seen usually in females. The aetiology is unclear, but drugs, hormones and viruses may contribute in genetically predisposed persons. Both discoid lupus erythematosus (DLE) and systemic lupus erythematosus (SLE) can affect the mouth, and the oral lesions can precede other manifestations in a minority.

- **DLE:** oral lesions are seen in up to 25% of those with cutaneous DLE, mainly in the buccal mucosa, gingiva and lip. Characteristic features include central erythema, white spots or papules, radiating white striae at margins and peripheral telangiectasia.
- **SLE:** oral lesions like those in DLE, but usually more severe ulceration. SLE may also be associated with Sjogren syndrome and, rarely, temporomandibular joint arthritis.

Diagnosis is by biopsy, blood picture and autoantibodies, especially crithidial (double-stranded DNA). Antinuclear factors are present in SLE, not in DLE. Biopsy shows the lupus band test with basement membrane zone deposits of IgG/IgM. There should be differentiation from lichen planus, leucoplakia (keratosis), galvanic-induced white lesions and carcinoma. Management includes:

- **DLE:** topical corticosteroids, cryosurgery or excision of localised lesions. There is a small predisposition to carcinoma.
- **SLE:** systemic steroids, azathioprine, chloroquine or gold.

Lyell's disease Toxic epidermal necrolysis (originally described in relation to staphylococcal infection).

Lyme disease Infection with *Borrelia burgdorferi* from deer ticks, causing rashes, fever, arthropathy and facial palsy. First recognised in the town of Lyme, Connecticut, USA, but prevalent worldwide.

Lymphangioma A hamartoma or benign neoplasm of lymphatic channels which presents as a colourless, sometimes finely nodular soft mass. Bleeding into lymphatic spaces causes sudden purplish discoloration. If in the tongue and extensive, it is a rare cause of macroglossia. If in the lip, it is a rare cause of macrocheilia. Diagnosis can be confirmed, if necessary, by excision biopsy.

Lymphomas Lymphomas (see also Burkitt's lymphoma, Hodgkin's disease and non-Hodgkin's lymphoma) are malignant tumours that originate in lymph nodes and lymphoid tissue: they can originate from any type of lymphocyte, but usually arise from B cells. HIV/AIDS and immunosuppression predispose to oral lymphomas. Painless enlarged cervical lymph nodes are the initial complaint in 50% of cases, but a lymphoma may occasionally produce primary or secondary tumours in the oral cavity. Lymphomas appear as swellings, often of the pharynx, palate, tongue, gingivae or lips. Involvement of Waldeyer's ring is common in non-Hodgkin's lymphomas.

Since patients with lymphoma develop a secondary immunodeficiency, herpes zoster, herpetic stomatitis and oral candidiasis may be seen. Diagnosis is made from clinical findings (generalised lymph node enlargement and hepatosplenomegaly), radiography (hilar and abdominal lymph node enlargement), lymphangiography, biopsy (lymph node or lesional). Treatment is mainly by chemotherapy.

Maffucci syndrome Multiple enchondromas, haemangiomas (often in the tongue), and risk of malignant chondrosarcomas.

MAGIC syndrome Mouth and genital ulcers and interstitial chondritis. A variant of Behçet syndrome.

Malignant melanoma A malignant tumour of melanocytes. It usually presents as a heavily pigmented (occasionally non-pigmented) macule or, later, as a nodule and ulceration. It may spread across several centimetres. The palate is most frequently affected, with spread to regional lymph nodes and then the blood stream. To differentiate naevi and other pigmented lesions, diagnosis is by wide excision biopsy. However, if melanoma is a significant possibility as judged clinically, the patient should be referred for immediate surgery.

Mantoux test Skin test for delayed-type hypersensitivity reaction to bacillus Calmette Guérin (BCG; for tuberculosis).

Marcus Gunn syndrome Jaw-winking syndrome (eyelid winks during chewing), with ptosis.

Marfan syndrome An autosomal-dominant condition prevalent among basketball and volleyball players, in which the patient is tall, thin and with arachnodactyly (long, thin spider-like hands). There may be dislocation of the lens, dissecting aortic aneurysms, aortic regurgitation, mitral valve prolapse, and the palate is occasionally cleft or with bifid uvula. Joint laxity is common. Recurrent dislocation of the temporomandibular joint and multiple dental cysts are less common oral complications.

Marie-Sainton syndrome Cleidocranial dysplasia.

Masseteric hypertrophy This may result from continual clenching of the jaws (bruxism).

Measles A common childhood exanthem, caused by the measles virus, with an incubation period of 7–14 days. Features include Koplik's spots (small white spots on the buccal mucosa during prodrome), rash (maculopapular), conjunctivitis, runny nose, cough, fever, malaise and anorexia. Diagnosis is from clinical features; a rising antibody titre is confirmatory. Differentiation is especially from thrush and Fordyce spots (not in children). Management is symptomatic.

Melkersson–Rosenthal syndrome The rare association of facial swelling, with facial palsy and fissured tongue.

Metastatic tumours in the jaws Although the jaws are not a common site for clinically obvious metastases it is probable that subclinical secondary deposits are not rare. The mandible is involved four times as frequently as the maxilla, especially in the premolar and molar region. Typical symptoms are pain and swelling, anaesthesia or paraesthesia, loosening of teeth, and occasionally pathological fracture. In up to one-third of patients the jaw lesions are the first manifestation of the tumour. The most common sites of the primary neoplasm are the bronchus, breast, kidney and thyroid gland, and metastases from these sites usually form destructive, osteolytic lesions. Metastases from the prostate tend to be osteoblastic and may be confused radiographically with chronic forms of osteomyelitis, Paget's disease and cemental lesions.

Miescher's cheilitis Oligosymptomatic orofacial granulomatosis or Crohn's disease clinically affecting the lip alone.

Migraine A recurrent headache, affecting women especially. Migraine appears to be related to 5-HT (serotonin) release, cerebral arterial dilatation and increased metabolic activity in the midbrain periaqueductal grey matter (the endogenous pain control pathway). Attacks may be precipitated by stress, alcohol, various foods such as ripe bananas or chocolate, or the contraceptive pill. Preceding warning symptoms (an aura) consist of visual, sensory, motor or speech disturbances. Visual phenomena are often of zig-zag coloured lights (fortification spectra) or transient visual defects. Headache, which is severe, is usually unilateral (hemicranial) and lasts for hours or days. Photophobia, nausea or vomiting may occur. The number, frequency and intensity of attacks decrease with increasing age and spontaneous remissions are not uncommon. Diagnosis is clinical. Management in acute attacks is aspirin or paracetamol (acetoaminophen), which may give some relief, or lysine acetylsalicylate with metoclopramide, which given early may abort an attack. Patients usually prefer to lie in a quiet,

dark room. Other treatments are directed at 5-HT receptors or uptake by blood platelets. Dihydroergotamine (interacts with 5-HT receptors) or sumatriptan (or another triptan-5-HT agonists which stimulate 5-HT receptors; see migrainous neuralgia, below) tricyclic antidepressants or phenelzine may also help intractable migraine. Prophylaxis may be achieved with a number of agents, including cyproheptadine, pizotifen, propranolol, tricyclics and calcium channel blockers.

Migrainous neuralgia Migrainous neuralgia (cluster headaches; histamine cephalgia; Sluder's headaches) is pain in the head and face, defined by the International Headache Society as unilateral excruciatingly severe attacks of pain principally in the ocular, frontal and temporal areas, recurring in separate bouts with daily or almost daily attacks for weeks or months usually with ipsilateral lacrimation, conjunctival injection, photophobia and nasal stuffiness and/or rhinorrhoea. Migrainous neuralgia is less common than migraine. Males are mainly affected and attacks often begin at about middle age. The pain is unilateral, occurs in attacks, is burning and 'boring' in character, and localised around the eye usually. Generally, the attacks last less than 1 hour (usually 30-45 minutes), commence and often terminate suddenly, and often awaken the patient at night or in the early hours of the morning (2-3 a.m.). This pain is associated on the affected side with profuse conjunctival watering and 'congestion', rhinorrhoea and nasal obstruction. There is vasodilatation in the extracranial carotid arteries and increased metabolic activity in the hypothalamus. Attacks are sometimes precipitated by hypoxaemia in REM sleep or at high altitudes, or where there is vasodilatation as induced by alcohol, histamine or nitroglycerin. Diagnosis is clinical but, as similar symptoms may be related to tumours around the cavernous sinus and craniospinal junction, computed tomography and/or magnetic resonance imaging are indicated. Migrainous neuralgia is managed with oxygen inhalations, and sumatriptan. Prophylaxis includes lithium, verapamil, nifedipine, diltiazem or ergotamine.

Mikulicz disease Salivary gland and lacrimal gland swelling, often related to Sjögren syndrome.

Mikulicz syndrome Salivary gland and lacrimal gland swelling related to malignant disease.

Mikulicz ulcer Minor aphthous ulceration.

Mixed connective tissue disease This may present with xerostomia, trigeminal neuropathy, oral ulceration or Sjögren syndrome.

Moebius syndrome A complex congenital anomaly involving multiple cranial nerves, affecting mainly the abducens (sixth) and facial (seventh)

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nerves, and often associated with limb anomalies. Muscle transplantation has been used to address the lack of facial animation, lack of lower lip support and speech difficulties.

Moon's molars Hypoplastic molars from congenital syphilis.

Mucocoeles Cystic lesions of minor salivary glands. Most are caused by trauma to the duct, leading to extravasation of mucus. This type of mucocoele is not, however, lined by epithelium, and therefore is not a true cyst. Occasional mucocoeles are caused by saliva retention. Most mucocoeles appear in the lower labial mucosa, buccal mucosa or ventrum of tongue. They are fluctuant bluish lesions and either resolve spontaneously or can be excised or removed with cryosurgery.

Minor salivary gland outlet obstruction is most commonly encountered when a mucocoele is present, although smoking and its accompanying nicotinic stomatitis produces transient palatal minor gland outlet obstruction also. Superficial mucocoeles may be seen in lichen planus.

Mumps Mumps (acute viral sialadenitis; epidemic parotitis) is a common acute infectious disease which principally affects the parotid salivary glands. Mumps is:

- caused by an RNA paramyxovirus
- transmitted by direct contact or by droplet spread from saliva
- characterised by a longish incubation period of 2–3 weeks
- followed by immunity to further attacks.

Typically the patient suffers an acute onset of:

- Painful salivary swelling (parotitis), usually bilaterally, although in the early stages only one parotid gland may appear to be involved. There is no significant xerostomia. In approximately 10% of cases the submandibular glands are also affected; rarely, these may be the only glands involved. Generally, the salivary swelling persists for about 7 days and then gradually subsides.
- Trismus.
- Fever.
- Malaise.

Mumps less commonly and mainly in adults has extrasalivary manifestations involving organs other than the salivary glands, including:

- orchitis; ensuing infertility is rare
- pancreatitis
- meningoencephalitis
- rarely, oophoritis and thyroiditis; ensuing infertility is rare.

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ing, since it has an appearance resembling neoplasia (pseudoepitheliomatous hyperplasia).

Nelson syndrome A rare condition with hyperpigmentation caused by ACTH overproduction in response to adrenalectomy, used for breast cancer.

Neumann's bipolar aphthosis The association of recurrent aphthae with genital ulceration; probably this is a stage in the development of Behçet syndrome.

Neurilemmoma (schwannoma) A rare benign neoplasm of neurilemmal cells of the nerve axonal sheath. It presents as a slowly enlarging painless mass, usually in the tongue. Multiple neurofibromas characteristic of von Recklinghausen's neurofibromatosis are present, but are more common in skin with café au lait hyperpigmentation. Neurofibromas occasionally undergo sarcomatous change. Mucosal 'neurofibromas' (plexiform neuro-mas) may be seen in multiple endocrine neoplasia type III syndrome (with medullary carcinoma of the thyroid). Diagnosis is by biopsy. Management is by excision.

Nikolsky sign A term meaning blistering, or the extension of a blister, on gentle pressure (seen in pemphigus and pemphigoid).

Noma Noma (cancrum oris; gangrenous stomatitis) may result from acute ulcerative gingivitis in malnourished, debilitated, or severely immunocompromised patients. Anaerobes, particularly *Bacteroides* (*Porphyromonas*) species and *Fusobacterium necrophorum*, have been implicated. Spreading necrosis penetrates the buccal mucosa, leading to gangrene and an orocutaneous fistula and scarring. Diagnosis is clinical; an immune defect should always be excluded. Management includes improving nutrition, systemic antibiotics and plastic surgery, as required.

Non-Hodgkin's lymphomas These are more common than Hodgkin's disease and generally have a poor prognosis, and a predilection for the gastrointestinal tract and central nervous system. Enlargement of cervical lymph nodes is often the first sign, but non-Hodgkin's lymphomas may occur in the faucial region. Lymphomas are a recognised complication of HIV infection and may be Epstein-Barr virus related.

Noonan syndrome Congenital short stature and webbed neck, sometimes with cardiac anomalies, pulmonary stenosis and cherubism.

Ollier syndrome Multiple enchondromas.

Orofacial-digital syndromes A group of inherited conditions manifesting with cleft lip and other facial anomalies, tongue clefts and multiple fraenae. Various dental defects, lingual and gingival nodules may be seen.

Orofacial granulomatosis Orofacial granulomatosis (OFG) (see Crohn's disease) is an uncommon condition seen mainly in adolescents and young adults and can manifest with facial and/or labial swelling, angular stomatitis and/or cracked lips, ulcers, mucosal tags, cobble-stoning or gingival hyperplasia. The aetiology is unknown, but a minority have gastrointestinal Crohn's or sarcoidosis; others have a postulated reaction to food or other antigens (e.g. benzoates or cinnamon), metals such as cobalt, or paratuberculosis or mycobacterial stress protein mSP65. Diagnosis is clinical, supported by blood tests, radiology, endoscopy, and biopsy to differentiate from sarcoid, Crohn's disease, tuberculosis and foreign body reactions. Management is to eliminate allergens and treat lesions with intralesional corticosteroids or, occasionally, systemic clofazimine or sulphasalazine.

Osler–Rendu–Weber disease Osler–Rendu–Weber disease (hereditary haemorrhagic telangiectasia; HHT) is an autosomal-dominant disorder where telangiectases are present orally, periorally and in the nose, gastrointestinal tract and occasionally on the palms. Telangiectases may bleed, and cryosurgery or laser treatment may be needed.

Ossifying fibroma This has features both of a developmental anomaly and a neoplasm. It presents as a painless, localised slow-growing, hard swelling of the jaw which radiographically is a well-defined radiolucency with a thin sclerotic margin containing irregular opaque masses. Histological examination shows little or no distinction between ossifying fibroma and fibrous dysplasia, except perhaps that a cellular, homogeneous calcified material is usually more obvious in ossifying fibroma. Distinction between ossifying fibroma and fibrous dysplasia, therefore, relies heavily on the localised nature and slow growth pattern of the ossifying fibroma. Surgical enucleation is curative.

Osteochondroma Osteochondroma (osteocartilaginous exostosis) arises from the epiphyseal region of bone as cartilage-capped bony outgrowths, usually in children. Lesions may be solitary, or multiple in the syndrome of hereditary multiple exostoses. In the jaws the most common site is the coronoid process. The solitary lesions are entirely benign, but in patients with multiple osteochondromas there is a significant risk of malignant change.

Osteogenesis imperfecta Osteogenesis imperfecta (brittle bone syndrome; fragilitas ossium) is the term given to a group of at least four types of inherited bone disorder characterised by excessive bone fragility and a number of extraskeletal connective tissue disorders. Affected children may have multiple rib fractures (giving a 'beaded' radiographic appearance) and shortened concertina-like long bones. The skull is soft and has multiple

Wormian bones. Fracture of limb bones following mild injury is the most common skeletal problem of such patients. Patients are usually of short stature, have grossly deformed limbs and deformities of the spine and trunk and often cannot walk. Some have dentinogenesis imperfecta.

Blue sclera occur in up to 90% of all osteogenesis imperfecta patients. Deafness is a common problem due to defective conduction of sound through the external and middle ear, a direct consequence of deformity of the associated bones. Hormones (calcitonin), vitamins (e.g. vitamin C or D), fluoride and flavonoids have, to date, been of little value and in most instances surgical intervention for skeletal deformities is needed.

Osteoid osteoma and osteoblastoma Benign tumours of bone which are uncommon in the skeleton generally and rare in the jaws. The microscopic features of these tumours are similar, but they have distinctive clinical and radiological features. Osteoid osteoma is usually seen in adolescents and young adults, most frequently in the femur and tibia. It is often painful, particularly at night. Osteoid osteoma has a characteristic radiographical appearance with a central radiolucent area or nidus surrounded by a rim of densely sclerotic bone of variable thickness. The nidus rarely exceeds 1 cm in diameter. Osteoid osteoma, on the other hand, shows progressive growth without the osteosclerotic rim and is rarely painful. Microscopically both lesions consist of a vascular stroma in which there are trabeculae of osteoid surrounded by numerous, and darkly staining, osteoblasts.

Osteoma This is a benign neoplasm of bone which grows by the continuous formation of lamellar bone; it should be distinguished from an exostosis. Osteomas are usually unilateral, painless, hard smooth swellings covered by normal oral mucosa. Multiple osteomas and polyposis coli are features of Gardner syndrome; the polyps in the large bowel may become malignant.

Osteomyelitis This literally means 'inflammation of the bone marrow', although sometimes the subperiosteal bone is mainly affected. Acute osteomyelitis primarily affects the mandible, usually affects adults and is essentially an osteolytic, destructive process, but an osteoblastic response is typical of sclerosing osteomyelitis. In children, proliferative periostitis may occur. Predisposing factors are sources from which bacteria can spread to bone:

- from local odontogenic infections (the commonest cause)
- from other adjacent structures (e.g. otitis media, tonsillitis, suppurative sialadenitis)
- haematogenous spread of organisms (this is rare in relation to the jaws).

When osteomyelitis of the mandible does occur, it may be a sign of an underlying debilitating disease, such as diabetes mellitus, an immune defect, or the effects of alcoholism: alternatively, it may be related to reduced vascularity such as after irradiation or in rare conditions such as Paget's disease or osteopetrosis. *Staphylococcus aureus* is the commonest organism causing osteomyelitis in the jaws, but streptococci (both α - and β -haemolytic) and anaerobic organisms (e.g. *Bacteroides* and *Peptostreptococci* species) are occasionally implicated.

In acute osteomyelitis the organisms excite an acute inflammatory response in the medullary bone and the consequent oedema and exudation within the rigidly enclosed bone marrow causes pus to be forced under pressure through the medullary bone. The pressure causes thrombosis of the intrabony blood vessels (i.e. the inferior dental artery), reducing the vascular supply to the bone, which then necroses. Eventually the pus bursts through the cortical plate to drain via sinuses in the skin or mucosa. Where pus penetrates the cortex it may spread subperiosteally, stripping the periosteum from the bone and thus further reducing the blood supply. Necrotic areas of bone become sequestra surrounded by pus and either spontaneously discharge or remain and perpetuate the infection. The periosteum which has been lifted from the underlying bone lays down new bone to form an involucrum encasing the infected and sequestered bone. The involucrum, although perforated by sinuses which drain pus, may prevent sequestra from being shed. Finally, if little new bone is formed, a pathological fracture may occur. Mandibular osteomyelitis presents with a deep-seated, boring pain, and swelling. Teeth in the affected segment are mobile and tender to percussion, and pus oozes from the gingival crevices. Once pus penetrates the cortical plate the pain improves and discharges intra- or extraorally, often through several sinuses. Labial anaesthesia is a characteristic feature because of pressure on the inferior alveolar nerve. The patient is often febrile and toxic with enlarged regional lymph nodes. Diagnosis is clinical, supported by radiographs which, in established cases, show marked bony destruction and sequestration but, since the radiographic changes are seen only after there has been significant decalcification of bone, early cases may not be detected and in these isotope bone scanning using technetium diphosphonate may show increased uptake. Blood tests show a leucocytosis with neutrophilia, and a raised erythrocyte sedimentation rate. Treatment is by antibiotic therapy and usually drainage. Management may be medical, surgical or a combination. Penicillin is still the drug of choice, but many staphylococci are now penicillin-resistant, and for these infections, flucloxacillin or fusidic acid may be used. Lincomycin and clindamycin also give high bone levels but, because of a high incidence of pseudo-membranous colitis, are now regarded as second-line drugs. Metronidazole gives good bone levels and

is indicated where anaerobic infection is suspected. Drainage of established pus follows the same guidelines used for other infections. When dead bone is exposed in the mouth, it can often be left to sequestrate without surgical interference, but sequestrectomy should be undertaken if the separated dead bone fails to discharge and decortication of the mandible may be needed in order to allow this and drainage.

Hyperbaric oxygen is an effective adjunct for recalcitrant osteomyelitis, especially where anaerobic organisms are involved.

Acute maxillary osteomyelitis This is seen rarely, and usually in infants, presumably because the lack of development of the antrum at this age makes the maxilla a dense bone.

Chronic osteomyelitis This presents with intermittent pain and swelling, relieved by the discharge of pus through longstanding sinuses. Bone destruction is localised and often a single sequestrum may be the source of chronic infection. Removal of the sequestrum and curettage of the associated granulation tissue usually produces complete resolution.

Focal sclerosing osteomyelitis This is usually asymptomatic and is revealed as an incidental radiographic finding. Most common in young adults it is usually associated with apical infection of a mandibular molar. Radiographically there is a dense, radio-opaque area of sclerotic bone related to the apical area, caused by formation of endosteal bone. This appears to be a response to low-grade infection in a highly immune host. Following tooth extraction the infection usually resolves (but the area of sclerotic bone often remains).

Diffuse sclerosing osteomyelitis A sclerotic endosteal reaction which, like focal sclerosing osteomyelitis, appears to be a response to low-grade infection. However, the area of bone involved is widespread and sometimes involves most of the mandible or occasionally the maxilla. Sometimes the infection arises in an abnormally osteosclerotic mandible, such as in Paget's disease, osteopetrosis or fibrous dysplasia. Intermittent swelling, pain and discharge of pus may go on for years. Management is difficult because of the extensive nature of the disease process. Long-term antibiotics, curettage and limited sequestrectomy all have their place.

Proliferative periostitis (Garre's osteomyelitis) This is more common in children than adults. The cellular osteogenic periosteum of the child responds to low-grade infection, such as apical infection of a lower first molar tooth, by proliferation and deposition of subperiosteal new bone. The subperiosteal bone may be deposited in layers, producing an onion-skin appearance radiologically, which can simulate Ewing sarcoma. The endosteal bone, however, may appear to be completely normal, but in severe cases also appears moth-eaten radiologically. Removal of the infective source is usually followed by complete resolution, although subsequent bone remodelling can take a considerable time.

Osteopetrosis Osteopetrosis (marble bone disease; Albers-Schonberg disease) is characterised by increased bone density with replacement of normal medullary bone by irregular avascular bone. Marrow is replaced by bone, and thus extramedullary sites such as the liver, spleen and lymph nodes develop haemopoietic function. Osteopetrosis is inherited in an autosomal-dominant or recessive manner. Patients with the autosomal-dominant form of osteopetrosis have good general health and a normal lifespan. There is no effective treatment for the recessive form: regular blood transfusions, steroids and splenectomy may correct the anaemia; cranial nerve decompression may be necessary and, if hydrocephalus develops, ventricular shunts may be required. However, most affected children die in the first decade of life, usually as a consequence of overwhelming infection or haemorrhage. The jaws, particularly the maxillae, are thickened and sclerotic and the paranasal sinuses are often reduced in size. Recurrent sinusitis and cranial nerve palsies (especially II, III, V, VII and VIII) are other orofacial problems of osteopetrosis. Children with the recessive form of osteopetrosis may have teeth with hypoplastic enamel, shortened roots and an increased susceptibility to caries. Eruption of teeth can be delayed or absent. Pathological fracture is common. As a consequence of the sclerotic bone, dental extractions can be difficult and the mandible also liable to fracture. The reduced vascularity of bone predisposes to postextraction osteomyelitis.

Osteoporosis A fairly common condition, characterised by the loss of both the organic matrix and the mineralised components of bone, although serum biochemistry is normal. The most common cause of osteoporosis is ageing, especially in females (hormonal), but drugs (especially corticosteroids) and several other disorders can also increase the rate of bone loss. The main clinical problem of osteoporosis is fracture of either the neck of femur or collapse of vertebral bodies. Osteoporosis has no notable oral manifestations, but may affect the jaws and predispose to fracture or periodontal bone loss. Osteoporosis is managed by treatment of the underlying disorder (where possible) and by use of stimulators of osteogenesis (fluoride, phosphate, sex hormones or parathyroid hormone) or inhibitors of bone resorption (e.g. calcium, vitamin D, bisphosphonates). Patients are encouraged to exercise and avoid long periods of inactivity.

Osteosarcoma An aggressive malignant neoplasm which typically affects young patients. Males are affected twice as frequently as females. Only rarely are the mandible or maxilla affected. The aetiology is largely unknown, although about 3% of patients with osteosarcomas have a history of irradiation for other lesions. It should be noted that there is another peak incidence of osteosarcoma in the over fifties, which probably represents the small but significant malignant change in patients with

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Pregnancy gingivitis An exacerbation of chronic gingivitis by pregnancy. Common mainly after the second month of pregnancy, pregnancy gingivitis presents with erythema, swelling and liability to bleed. Occasionally, a proliferative response at the site of a particularly dense plaque accumulation leads to a pregnancy epulis (pyogenic granuloma). This is a soft, red or occasionally firm swelling of the dental papilla. It may be asymptomatic unless traumatised by biting or toothbrushing. Oral hygiene should be improved. If asymptomatic, an epulis should be left alone – it may regress after parturition. If symptomatic, excision biopsy is indicated.

Progeria A collagen abnormality causing dwarfism, premature ageing and a characteristic facial appearance due to a disproportionately small face with mandibular retrognathia and a beak-like nose. Death occurs usually in the mid-teens.

Pseudoxanthoma elasticum An autosomal-recessive condition of progressive calcification of elastic tissue in the retina, skin, cardiovascular system, and oral lesions of yellow plaques, somewhat resembling Fordyce spots.

Psoriasis Psoriasis of the oral mucosa is rare and is characterised by erythema, white or greyish plaques, and lesions similar to erythema migrans. Gingival involvement in the form of desquamative gingivitis may rarely be seen. Biopsy of lesional tissue, with histological and immunostaining examination are essential to the diagnosis. Topical corticosteroids may be helpful in these cases.

Purpura The red or brown pinpoint lesions (petechiae) or diffuse bruising (ecchymoses) mainly at sites of trauma, especially in persons with blood platelet disorders or where there is trauma such as in fellatio or vomiting in bulimia. Lesions do not blanch on pressure (cf. haemangioma). Occasional small traumatic petechiae are seen at the occlusal line in otherwise healthy patients. Platelet deficiency is usually idiopathic (autoimmune), sometimes in infectious mononucleosis, HIV disease, rubella or renal disease. Localised oral purpura may appear for no apparent reason ('angina bullosa haemorrhagica'). Diagnosis is from a blood picture and haemostatic function to differentiate from haemangiomas, telangiectasia and Kaposi sarcoma. Treatment is of the underlying cause.

Pyogenic granuloma A possibly reactive vascular lesion. Intraoral lesions are sometimes associated with pregnancy. Typically, a pyogenic granuloma is a small (<3 cm) red painless mass that bleeds easily, ulcerates and grows rapidly and is frequently seen on the gingival margin or tongue. Treatment is excision to exclude angiomatous proliferations, chancre, carcinoma or Kaposi sarcoma.

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gut. Renal disease impairs the conversion of vitamin D to dihydroxycholecalciferol and consequently can lead to 'renal rickets'. Rickets is clinically characterised by a spectrum of bony deformities, which range from mild bowing of the long bones of the legs to gross skeletal deformity and dwarf-ism. Osteomalacia causes generalised bone pain and tenderness, vertebral collapse, pelvic deformities and myopathy. Correction of any underlying clinical disorder is required and supplements of one of the metabolites of cholecalciferol are the usual lines of therapy for osteomalacia and rickets.

Rieger syndrome Congenital ocular anomalies, iridal hypoplasia, glaucoma and blindness, maxillary hypoplasia and dental hypoplasia with oligo- and microdontia.

Riley-Day syndrome Inherited familial dysautonomia; sympathetic dysfunction, enlarged salivary glands, sialorrhoea and self-mutilation, seen particularly in Ashkenazi Jews.

Romberg syndrome (hemifacial atrophy) Progressive atrophy of the soft tissues of half the face, associated with contralateral Jacksonian epilepsy and trigeminal neuralgia. It starts in the first decade and lasts about 3 years before it becomes quiescent. Rarely, half the body may be affected.

Rosai-Dorfmann syndrome Rosai-Doorman syndrome (sinus histiocytosis with massive lymphadenopathy or Destombes-Rosai-Dorfman syndrome) is a benign, non-Langerhans cell, histiocytic proliferative disorder that primarily affects lymph nodes.

Rothmund-Thomson syndrome Congenital poikiloderma, hypogonadism, dwarfism, cataracts and microdontia.

Rubella A highly infectious viral disease that causes cervical lymphadenopathy, a macular rash starting on the face and behind the ears, mild fever, sore throat and, occasionally, palatal petechiae. Transplacental infection of the foetus may cause high-tone deafness, learning disability, blindness, cardiac defects or death.

Rubinstein-Taybi syndrome Rubinstein-Taybi syndrome (broad thumb-great toe syndrome) consists of short stature with a small head size, and developmental delay. The most striking physical feature is broad, sometimes angulated thumbs and first toes. The facial features include a prominent beaked nose and down-slanting eyes. Undescended testes occur in males.

Rutherford syndrome Corneal dystrophy, gingival fibromatosis and delayed tooth eruption.

Ruvalcaba–Myrhe–Smith syndrome Congenital macrocephaly, learning disability, intestinal polyps, pigmented macules on the penis, tongue polyps.

Sabin–Feldmann test Serological test for toxoplasmosis.

Saethre–Chotzen syndrome An autosomal-dominant craniosynostosis associated with cleft palate as well as other disturbances of the facial skeleton and extremities.

Salivary fistula An abnormal communication between the gland or ducts and skin or mucous membrane. Internal fistulae are uncommon and asymptomatic. Trauma to the major glands or duct may (rarely) cause a persistent external fistula that is unpleasant and may lead to infection. Surgical repair is then indicated.

Salivary neoplasms These are uncommon. A wide range of different neoplasms can affect the salivary glands, but most are epithelial neoplasms, present as unilateral swelling of the parotid and are benign. The 'rule of nines' is an approximation that states that 9 out of 10 salivary gland tumours:

- affect the parotid
- are benign
- are pleomorphic salivary adenomas (PSAs).

The next most common is carcinoma. Other neoplasms of major salivary gland are usually monomorphic adenomas (such as adenolymphomas), mucoepidermoid tumours or acinic cell tumours.

- Parotid tumours are largely PSAs.
- Submandibular gland tumours are also usually PSAs; malignant neoplasms contribute up to one-third of all submandibular tumours.
- Sublingual gland tumours are exceedingly rare, but virtually all are malignant.
- In minor salivary glands, PSAs are again the most common neoplasm, but only account for around 50%, and most of the remainder are malignant tumours, such as carcinomas and adenoid cystic carcinomas. Minor salivary gland tumours most commonly arise in the palate, but may be seen in the buccal mucosa or upper lip, rarely in the tongue or lower lip.

Salivary gland tumours are more common in certain geographical locations. Inuits, for example, have an increased prevalence and this has been suggested to be related to Epstein–Barr virus infection. There is a correlation between salivary gland and breast cancer. The aetiology is unknown, but salivary gland tumours have been increased in incidence in:

- survivors of the atomic explosions in Japan
- the use of iodine-131 in the treatment of thyroid
- following radiotherapy to the head and neck.

The main clinical feature of a neoplasm is salivary gland swelling. A long history of gradual gland enlargement suggests a benign process while pain or facial nerve palsy are ominous and suggest carcinoma. Clinical examination may reveal an obvious swelling in the case of the parotid outlining the gland anteriorly to the ear, and causing eversion of the ear lobe. However, some tumours are small and the presentation may be of pain only.

The World Health Organisation classification (1991) is the most widely used classification of salivary gland neoplasms and the epithelial tumours, which are the most important, can be memorised by the mnemonic 'A Most Acceptable Classification':

- adenomas
- mucoepidermoid tumour – intermediate (see below)
- acinic cell tumour – intermediate (see below)
- carcinomas and other neoplasms.

The more important neoplasms only are discussed here.

Pleomorphic adenoma (mixed salivary gland tumour) PSA is:

- The most common salivary gland neoplasm.
- Usually a slow-growing, lobulated, rubbery swelling with normal overlying skin, but a bluish appearance if intraoral.
- Usually benign. However, it recurs if excision is inadequate. The tumour is poorly encapsulated and parotid adenomas are in intimate relationship with the facial nerve, both of which make complete excision difficult to achieve.

Pleomorphic adenoma appears to originate from ductal epithelium, which proliferates to contribute many duct-like spaces, sheets of epithelial cells and sometimes areas of squamous metaplasia. There are also areas reminiscent of connective tissue such as cartilage. The admixture of epithelial elements with what resembles fibrous, myxoid or cartilage tissue, leads to the name 'mixed tumour'. These lesions usually have a thin fibrous capsule, but this is not complete and neoplastic cells may be seen in or outside the capsule.

Malignant change is uncommon, but is suggested clinically by:

- rapid growth
- pain
- fixation to deep tissues
- facial palsy.

Malignant change is shown by obvious malignant features within the benign cellular picture.

Warthin's tumour (papillary cystadenoma lymphomatosum or adenolymphoma) This tumour:

- is found virtually only in the parotid
- accounts for about 1 in 10 parotid tumours
- is benign.

Columnar cells surround lymphocytes in a folded (papillary) lining to cystic spaces.

Oncocytoma Oncocytoma (oncocytic or oxyphil adenoma):

- is found virtually only in the parotid
- is extremely rare
- affects mainly the elderly
- is benign.

The characteristic of this tumour is that it consists of cords of large eosino-philic cells with small nuclei (oncocytes).

Acinic cell carcinoma Acinic cell tumours are:

- very rare
- usually benign, although all grades of malignancy have been reported.

Acinic cell tumours comprise large cells with a granular basophilic cytoplasm with holes between some cells. The cells resemble serous cells of normal salivary glands.

Mucoepidermoid tumour This tumour:

- accounts for up to 10% of salivary gland tumours
- is slow-growing
- is benign or of low-grade malignancy.

The mucoepidermoid tumour consists of large pale mucus-secreting cells (hence 'muco') surrounded by squamous epithelial cells (hence 'epidermoid').

Adenoid cystic carcinoma Adenoid cystic carcinoma (cylindroma) is:

- slow growing
- malignant, with a tendency to infiltrate, spread perineurally, and metastasise.

Rounded islands of small darkly staining cells surrounding multiple clear areas of varying size (Swiss-cheese appearance) are characteristic.

Other salivary tumours These include:

- **Non-epithelial tumours** (e.g. juvenile haemangioma).
- **Malignant lymphomas** are the next most common neoplasms found in salivary glands. Sjögren syndrome is recognised as predisposing to lymphomas which have arisen in up to 6% of patients over 10 years in some studies. An intermediate stage between the salivary gland swelling in Sjögren syndrome and lymphomas is termed the 'benign lymphoepithelial lesion', a histological rather than a clinical condition. It has recently been suggested that the lymphoepithelial lesion represents a localised lymphomatous process. HIV disease also predisposes to lymphomas, mainly non-Hodgkin's lymphomas, which are Epstein-Barr virus-related.
- **Secondary tumours.**
- **Unclassified tumours.**
- **Tumour-like lesions** (benign lymphoepithelial lesion, sialosis, oncocytosis)

Diagnosis of salivary gland neoplasms

- A swelling, especially if persistent may be a neoplasm.
- A detailed history and examination are essential.
- The diagnosis can only be firmly established by biopsy. Preoperative needle biopsy has a high tumour detection rate in experienced hands, more if computed tomography (CT) or ultrasound-guided, although some advocate leaving this until perioperatively if malignancy is likely, because tumour cells can be seeded in the needle track.
- Ultrasonography is useful, non-invasive and readily available.
- Sialography may reveal a filling defect or gland displacement, but is a relatively imprecise and non-specific
- CT or magnetic resonance imaging (MRI) alone, or in conjunction with sialography, are a more sensitive means of tumour detection.
- MRI can be useful to delineate the lesion.

Management of salivary gland neoplasms

- Early detection carries a good prognosis.
- The treatment of choice is surgical excision; the main hazard is facial palsy.
- Even PSAs require early removal since, in some cases, carcinoma arises.
- Some malignant salivary neoplasms, such as adenoid cystic carcinoma, invade bone and neural tissues preferentially and wide excision is required.
- Radiotherapy is sometimes used as an adjunct for malignant tumours.

Salivary duct obstruction Salivary duct obstruction (obstructive sialadenitis) is not uncommon and is usually caused by:

- a calculus (stone)
- rarely oedema from irritation of the duct by, for example, a denture clasp

- 'physiological' duct obstruction due either to duct spasm or an abnormal passage of the parotid duct through the buccinator or in relation to the masseter muscles
- mucus plug
- neoplasm
- stricture.

Duct obstruction can cause salivary gland swelling and pain. Prolonged duct obstruction produces atrophy particularly of serous acini, such as in the parotid gland.

- Most obstructions are calculi in the submandibular duct.
- A history of painful salivary gland swelling just before, or at, mealtimes is classical of obstruction.
- In older patients, this history is not always obtained and there may be only dull pain over the affected gland, referred elsewhere.
- It is occasionally possible clinically to determine the cause of major duct obstruction if a calculus is palpable or visible.
- In other cases, plain radiographs may reveal a calculus if it is radio-opaque. Two views at 90° are required.
- Sialography should help differentiate the various causes of major duct obstruction: intraductal or ductal causes are usually readily seen, but 'physiological' obstructions require pressure-monitored sialographic techniques for detection.
- Extraductal causes of obstruction may be clinically obvious or apparent only on sialography or combined CT sialography.
- CT, MRI or ultrasonography are occasionally required.

Intraductal and ductal causes of duct obstruction are usually correctable by the removal of the cause (e.g. calculus or mucus plug) or, in a benign stricture, by repeated duct dilatation with a lacrimal duct dilator.

Sarcoidosis An uncommon chronic granulomatous reaction, of unknown aetiology. Prevalent particularly in black females, it presents with cervical lymphadenopathy, enlarged salivary glands and xerostomia. Heerfordt syndrome (salivary and lacrimal swelling, facial palsy and uveitis), mucosal nodules, gingival hyperplasia or labial swelling are rare. The oral lesions may occasionally precede systemic involvement. Biopsy of minor salivary glands reveals granulomas in up to 20% of patients, particularly in those with hilar lymphadenopathy. Diagnosis is by biopsy, chest radiography, gallium scan, raised serum angiotensin converting enzyme and adenosine deaminase, to differentiate from Crohn's disease, tuberculosis and foreign body reactions. Management is with intralesional corticosteroids; systemic steroids if the lung or eye are involved.

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Diagnosis of sialadenitis is on clinical grounds. Investigations may be needed to exclude hyposalivation. Sialography may be needed later to establish whether there are any ductal or other lesions that predispose to the infection. Management is as follows:

- Collect pus for a stained smear, culture and antibiotic sensitivity testing.
- Axillary temperature should be noted.
- Evidence of cervical lymphadenopathy should be sought.
- Antibiotic therapy should be commenced orally. The antibiotic of choice is flucloxacillin, with erythromycin as an alternative if the patient is penicillin allergic.
- Any fluctuant swelling should be surgically drained.
- Supportive therapy, such as ensuring an adequate fluid intake, analgesics and attention to good oral hygiene, is important.

Once the acute condition has resolved, sialography should be undertaken to identify correctable factors such as mucus plugs, strictures or calculi.

Chronic bacterial sialadenitis This may develop following acute sialadenitis, particularly if treatment is inadequate, or predisposing factors are not eliminated. Unfortunately, serous acini may atrophy when salivary outflow is chronically obstructed and this further reduces salivary function.

Sialadenosis An uncommon, benign non-inflammatory, non-neoplastic bilaterally symmetrical and painless enlargement of salivary glands. A variety of causes of sialadenosis (sialosis) are recognised, most associated with autonomic neuropathy, including:

- **Drugs:**
 - alcohol abuse with or without accompanying liver cirrhosis
 - sympathomimetic agents such as isoprenaline
 - phenylbutazone, isoprenaline, antithyroid drugs and phenothiazines.
- **Endocrine conditions:**
 - diabetes mellitus
 - pregnancy
 - acromegaly
 - following oophorectomy.
- **Nutritional disorders:**
 - malnutrition
 - anorexia nervosa
 - bulimia
 - cystic fibrosis and pancreatitis.

Sialadenosis usually affects both parotids. Clinically there is soft, painless general enlargement of the involved glands. A useful guide to whether the patient is simply obese or has parotid enlargement is to observe the out-

ward deflection of the ear lobe which is seen in true parotid swelling. The diagnosis of sialadenosis is one of exclusion, based mainly on history and clinical examination. Investigations indicated may include:

- Blood tests: for raised glucose levels or abnormal liver function.
- Sialography: reveals enlarged but otherwise normal glands, although salivary secretion is not impaired. However, if a bilateral space-occupying lesion such as a salivary neoplasm, cyst or lymphoid neoplasm presents difficulties in differentiation from sialadenosis, sialography or magnetic resonance imaging may help.
- Ultrasound: rarely, a bilateral space-occupying lesion such as a salivary neoplasm, cyst or lymphoid neoplasm may present difficulties in differentiation from sialadenosis, and then ultrasound may help.
- Biopsy is rarely needed. The affected glands show acinar hypertrophy, which appears related to an autonomic neuropathy.
- Sialochemistry shows raised potassium and calcium levels, which are not found in other causes of parotid enlargement.

No treatment is available. If investigations have revealed a likely cause such as alcoholism or diabetes, then sialadenosis may resolve when alcohol intake is reduced or glucose control is instituted.

Sipple syndrome Multiple endocrine neoplasia (MEN) type 3 (MEN 3; sometimes called 2b) affecting several endocrine glands with multiple mucosal neuromas, pheochromocytoma and medullary thyroid carcinoma (calcitonin levels raised).

Sjögren–Larsson syndrome Congenital ichthyosis, learning disability, cerebral palsy and indifference to pain.

Sjögren syndrome Xerostomia and keratoconjunctivitis sicca, i.e. dry mouth and dry eyes.

Sluder syndrome This is migrainous neuralgia.

Smith–Lemli–Opitz syndrome Congenital short stature, learning disability, syndactyly, urogenital and maxillary anomalies.

Solitary bone cysts Lesions that occur most commonly in the long bones, but may also be found occasionally in the jaws. Their cause is speculative, but, they may arise after trauma to the bone when an intramedullary haematoma forms and then degenerates rather than progressing to normal healing. Haemorrhagic bone cysts are generally painless and expansion is uncommon, the lesions usually being coincidentally discovered during radiographic examination. They are seen most often in the posterior body of the mandible in young persons. Clear or blood-stained fluid may be found within the bony cavity, but preoperative aspiration may at times not

yield any product. Radiologically there is a well defined translucency with a scalloped appearance around the apices of the teeth which are vital. Surgery is undertaken in order to make a definitive diagnosis. There is no detectable cyst lining and sometimes only a thin fibrous membrane. Curettage produces bone fragments and connective tissue sometimes with granulation tissue. However, such surgical opening of the cavity usually leads to spontaneous resolution.

Stafne bone cavity This is not a cyst of the jaw, but an ectopic inclusion of salivary tissue, often from the submandibular gland. Radiography shows a radiolucency resembling a cyst. No treatment is indicated, but when a diagnosis cannot be made by non-invasive means such as sialography, or when serial radiographs show an increase in cavity size, exploratory surgery is indicated.

Stevens–Johnson syndrome This is severe erythema multiforme, precipitated particularly by drugs and infections.

Still syndrome This is juvenile rheumatoid arthritis.

Sturge–Weber syndrome Sturge–Weber syndrome (encephalotrigeminal angiomas) is congenital hamartomatous angioma of the upper face (naevus flammeus), oral mucosa and underlying bone (with hemihypertrophy of bone and accelerated eruption of associated teeth), extending intracranially to cause convulsions, and contralateral hemiplegia and intracerebral calcifications and sometimes learning disability.

Subepithelial immune blistering diseases These include pemphigoid variants, dermatitis herpetiformis, linear IgA disease and chronic bullous disease of childhood.

Submucous fibrosis Submucous fibrosis (oral submucous fibrosis (OSMF)) is virtually only a disease of adults from Asia, related to the use of areca nuts, now also found in Pan Masala and Gutkha. It is possible that it is due to the copper content which increases collagen cross-linking. Tight vertical bands in the buccal mucosa may progress to severely restricted oral opening. OSMF can also affect the soft palate or tongue and produces epithelial atrophy. There is a premalignant potential – carcinoma develops possibly in up to 8%. It is usually easily diagnosed, since it is extremely rare in people not of Asian extraction. There is a history of betel chewing and no history of other injury or surgery. Diagnosis is from the clinical features, biopsy and haematology. Often anaemia is present. Management is to stop use of areca nut. Asymptomatic cases should be observed only. Symptomatic cases with restricted opening may respond to exercises, intralesional corticosteroids, penicillamine, interferon or surgery (usually excision of the ‘scarred’ tissue in the cheeks and transposition of bilateral palatal island flaps).

Superior vena cava obstruction Obstruction of cardiac venous return, usually by lung cancer, may produce oedema and cyanosis of face, neck and arms.

Surgical emphysema Escape of air into the tissues, usually after using an air rotor to section a tooth for removal, may give rise to diffuse swelling, which characteristically is painless, but gives rise to crepitus on palpation.

Sutton's ulcers This is major aphthae.

Sweet syndrome Acute neutrophilic dermatosis; red mucosal lesions and ulcers.

Syphilis Syphilis is a sexually transmitted infection caused by *Treponema pallidum*. Other treponematoses, including yaws, bejel and pinta, are rare in the developed world.

Congenital syphilis This manifests with frontal bossing, saddle nose, hutchinsonian incisors, Moon's or mulberry molars and rhagades. Learning disability, interstitial keratitis, deafness, sabre tibiae and Clutton's joints may be seen.

Acquired syphilis This is predominantly an infection of the sexually promiscuous (prostitutes, men who have sex with men, travellers, armed forces). Diagnosis is by direct smear of primary and secondary stage lesions. Serology becomes positive late in the primary stage. Penicillin by injection (or erythromycin or tetracycline). Incubation period 9–90 days.

Primary syphilis (Hunterian or hard chancre) This is a small papule which develops into a large painless indurated ulcer, with regional lymphadenitis. A chancre heals spontaneously in 1–2 months. Rare on the lip (upper) or intraorally – usually the tongue. *Treponema pallidum* in smear (dark-field examination). Serology is positive late in this stage. Differentiate from trauma, herpes labialis, pyogenic granuloma and carcinoma.

Secondary syphilis This presents with oral lesions: mucous patches, split papules or snail-track ulcers, which are highly infectious. Rash (coppery coloured typically on palms and soles), condylomata lata and generalised lymph node enlargement can also be present.

Tertiary syphilis This may cause glossitis (leucoplakia) and gumma (usually midline in the palate or tongue). These are non-infectious, and may be associated with cardiovascular complications (aortic aneurysm) or neurosyphilis (tabes dorsalis, general paralysis of the insane, Argyll–Robinson pupils).

Takayasu's disease Pulseless aorta and large arteries.

Tetracycline staining Tetracycline staining of the teeth may be seen if tetracyclines are given to pregnant or nursing mothers, when they can

cause brown discoloration of the developing dentition, or when given to children under the age of 12 years (Fig. 37.6).



Figure 37.6 Tetracycline-stained teeth; still occasionally seen

Thibierge–Weissenbach syndrome The CREST syndrome – scleroderma with calcinosis and ischaemia.

Thyroglossal cyst This arises from remnants of the thyroglossal duct and is midline at any point between the tongue and thyroid gland, and moves up on protrusion of the tongue. The cyst may cause dysphagia or become infected. It should be surgically removed.

TORCH syndrome Toxoplasmosis, Other infections, Rubella, Cytomegalovirus, Herpes simplex induced fetal abnormalities

Torus palatinus and mandibularis Developmental benign exostoses with a smooth or nodular surface. Tori are common conditions of no consequence apart from occasionally interfering with denture construction. Torus palatinus occurs in the centre of the hard palate. This is of variable size and may have a smooth or nodular surface (Fig. 37.7). The torus is more common in Mongoloid races and may become more apparent with increasing age. Torus mandibularis is lingual to the lower premolars and usually bilateral. Although there is no association with torus palatinus, the torus mandibularis is also seen most commonly in mongoloids and is more apparent with increasing age. The tori are usually located bilaterally, lingual to the mandibular premolars (Fig. 37.8).

Toxic epidermal necrolysis Toxic epidermal necrolysis (TEN; Lyell's disease) is a rare clinicopathological entity, with a high mortality, characterised by extensive detachment of full-thickness epithelium. The distinction from erythema multiforme is unclear, but most cases of TEN are drug-induced and the lesions are extremely widespread.

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Toxoplasmosis This is caused by the parasite *Toxoplasma gondii*, which infects members of the cat family who excrete it in faeces. *T. gondii* survives in soil for up to 1 year, and infection is generally by ingestion of cysts or oocysts, which are present in up to 10% of lamb and 25% of pork used for human consumption. In normal healthy patients symptomatic toxoplasmosis manifests as:

- Glandular fever syndrome, with a negative Paul-Bunell test.
- Ocular toxoplasmosis with chorioretinitis.
- Transplacental transmission may result in foetal defects.

In immunocompromised patients such as those with HIV/AIDS, *T. gondii* may produce CNS involvement.

Toxoplasmosis is diagnosed by detection of serum antibodies by the Sabin-Feldmann dye test, indirect haemagglutination or IgM fluorescent antibody tests, and isolation of *T. gondii* or histological demonstration of trophozoites. Toxoplasmosis is treated with pyrimethamine and sulphadiazine.

Treacher-Collins syndrome Treacher-Collins syndrome (mandibulofacial dysostosis) is an autosomal-dominant defect in the first branchial arch with downward sloping (anti-mongoloid slant) palpebral fissures, hypoplastic malar complexes, mandibular retrognathia, deformed pinnae, hypoplastic sinuses, colobomas in the outer third of the eye, and middle and inner ear hypoplasia (deafness).

Trichodontoosseous syndrome Autosomal dominant; kinky hair, amelogenesis imperfecta; taurodont molars and brittle nails.

Trotter syndrome Acquired unilateral deafness, pain in the mandibular (third) division of the trigeminal nerve, ipsilateral palatal immobility, and trismus due to invasion of the nasopharynx and the trigeminal nerve by a malignant tumour. Pterygopalatine fossa syndrome is a similar condition, where the first and second divisions of the trigeminal nerve are affected.

Tuberculosis An infection with mycobacteria, usually *Mycobacterium tuberculosis*, but rarely atypical mycobacteria, e.g. *M. avium-intracellulare*, *M. scrofulaceum* and *M. kansasii*, especially in HIV infection. Uncommon, tuberculosis is usually pulmonary and seen mainly in alcoholics, diabetics, patients with immune defects (including HIV infection), and certain racial groups (e.g. Asian). Clinical features may include a single chronic ulcer on dorsum of tongue associated with (postprimary) pulmonary infection. Diagnosis is confirmed by biopsy, sputum culture, tuberculin testing and chest radiography. Management is with combination chemotherapy. Treatment is started with three drugs in combination in order to avoid the emergence of bacterial resistance, and is then continued with two or more

antibiotics, usually from the following: rifampicin, isoniazid, ethambutol or streptomycin. Chemotherapy is usually effective treatment, but must be given for prolonged periods and, if chemotherapy is less than adequate, bacterial resistance readily develops. Multi-drug resistance is increasing in HIV/AIDS.

Tularemia This is caused by the coccobacillus *Francisella tularensis*. The epidemics are thought to be waterborne. The majority of the patients are young and female. In most of the cases the disease presents itself in oropharyngeal form, with fever and tonsillopharyngitis and cervical lymphadenopathy. Streptomycin is given to most patients in combination with tetracycline, doxycycline or chloramphenicol.

Turner's tooth Hypoplastic tooth due to damage to the developing tooth germ.

Tzanck cells Abnormal epithelial squames in pemphigus or herpetic infections.

Ulcerative colitis This may present with persistent diarrhoea, which is frequently painless, with passage of blood and mucus in severe cases, iron deficiency anaemia, weight loss, and mucosal pustules (pyostomatitis vegetans), irregular chronic ulcers and aphthae. Diagnosis is by biopsy, full blood picture, sigmoidoscopy and barium enema. Management is with haematinics for any secondary deficiencies; topical corticosteroids may be helpful; as may sulphasalazine, or corticosteroid enemas.

Von Recklinghausen's disease Multiple neurofibromas with skin pigmentation, skeletal abnormalities and central nervous system involvement.

Von Willebrand's disease A common bleeding disorder caused by defective blood clotting factor VIII and platelet dysfunction.

Waardenburg syndrome Congenital heterochromia iridis (different coloured eyes), deafness, and white forelock, with prognathism.

Waldeyer's ring Lymphoid tissue surrounding the entrance to the oropharynx (tonsils and adenoids).

Warthin's tumour A benign salivary gland neoplasm – adenolymphoma or papillary cystadenoma lymphomatosum.

Wegener's granulomatosis Idiopathic disseminated malignant granulomatous disorder affecting the lungs, kidneys and occasionally the mouth, sometimes related to *Staphylococcus aureus*. It is a rare, potentially lethal disorder in which there is necrotising granulomatosis initially of the respiratory tract followed by widespread arteritis of small vessels and renal damage. A painless progressive swelling of the gingiva in a

previously healthy mouth, particularly associated with swollen inflamed papillae, should arouse suspicion of this condition. The gingival enlargement may have a fairly characteristic 'strawberry-like' appearance. Diagnosis is supported by biopsy and anti-neutrophil cytoplasmic antigens (ANCA). Management is with antimicrobials, cytotoxic agents or radiotherapy.

Werner syndrome Congenital alopecia, dwarfism, senility, early atherosclerosis, delayed tooth eruption and mandibular hypoplasia.

White sponge naevus White sponge naevus (pachyderma oralis, white folded gingivostomatitis) is a rare autosomal-dominant defect of keratin causing a benign familial disorder with lesions, typically:

- symptomless
- white
- shaggy or folded or wrinkled
- bilateral
- seen in the buccal mucosa.

Lesions are sometimes seen in other oral sites especially the tongue, the floor of the mouth, or elsewhere, or in the:

- nose and upper respiratory tract
- pharynx
- oesophagus
- genitals
- anus.

The family history and examination are usually adequate to make the diagnosis, but there may be confusion with other white lesions, when a biopsy is indicated.

William syndrome A genetic disorder characterised by mild learning disability, unique personality characteristics, distinctive facial features, and cardiovascular disease (elastin arteriopathy). A range of connective tissue abnormalities is observed and hypercalcaemia and/or hypercalciuria are common.

Wiskott–Aldrich syndrome X-linked recessive immunodeficiency with thrombocytopenic purpura, infections, eczema (TIE syndrome) and lymphoreticular malignancies.

Witkop's disease This is hereditary benign intraepithelial dyskeratosis – seen mainly in parts of the USA.

Zimmerman–Laband syndrome See Laband syndrome).

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SECTION V

PDFFREE COMUNIDAD ODONTOLÓGICA

Relevant other Systemic Disorders

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38

PDFREE COMUNIDAD ODONTOLOGICA

Human Immunodeficiency Virus Infection

Human immunodeficiency virus disease

Infection with the RNA retroviruses known as human immunodeficiency viruses (HIV) – formerly termed ‘human T lymphotropic virus III’ (HTL-III) – produces HIV infection which eventually results in damage to T lymphocytes, especially those that are CD4⁺, and thus causes immunodeficiency. This predisposes to infection with fungi, viruses, mycobacteria or parasites, and the appearance of diseases, at which time the condition is termed ‘HIV disease’. This then progresses over time to the acquired immune deficiency syndrome (AIDS), defined as a CD4⁺ T-lymphocyte count at or below 200 cells/μl in the presence of HIV infection.

Incidence

AIDS was first recognised in the USA in the early 1980s, although the infection has subsequently been recognised in Africa some decades previously. The epidemic has exploded worldwide, largely in the socially excluded and in the developing world where HIV/AIDS is a leading cause of death in young adults and is increasing in children. The incidence worldwide varies widely to a high of around 50% in some populations in sub-Saharan Africa.

Age

Worldwide, young adults continue to be the age group mainly affected, but the number of cases in children continues to rise, largely through the increasing prevalence of infection in pregnant females.

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HIV-1 is by far the most common worldwide

HIV-2 is spreading from West Africa mainly.

- Infection with HIV infects various cells with CD4 receptors and damages mainly CD4⁺ T-helper lymphocytes and brain glial cells. In healthy persons aged 5 years and older, with normally functioning immune systems, the CD4⁺ T-cell counts usually range from 500 to 1500 cells/ μ l. In HIV infection, the CD4 cell count eventually falls (and there is a falling ratio of CD4/CD8 cells) and there is progressive immune deficiency and dementia.
- T-cell-mediated immune protection thus diminishes, and patients become predisposed to infection with yeasts and fungi, viruses, mycobacteria and parasites.
- Infections result, some from organisms that become opportunistic pathogens but are commensal (i.e. they cause no or little obvious harm) in the immunocompetent host; others are acquired from the environment (exogenous pathogens).

Opportunistic pathogens include *Candida* species and other fungi, and some herpesviruses – especially herpes simplex virus (HSV), varicella zoster virus, Epstein-Barr virus (EBV), cytomegalovirus (CMV) and human herpesvirus-8 (HHV-8).

Exogenous pathogens such as *Pneumocystis carinii*, tuberculosis and atypical mycobacteria such as *Mycobacterium avium-intercellulare*, and the parasite *Toxoplasma gondii* may cause serious disease.

Some viruses may cause neoplasms; HHV-8 causes Kaposi sarcoma and EBV causes lymphomas. Some human papilloma viruses (HPV) may cause cervical, anal and oropharyngeal carcinoma.

Clinical features

Acute HIV infection

Acute HIV infection is unrecognised in the majority, but symptomatic in the 4- to 7-week period of rapid viral replication immediately following exposure in one-third to one-half of those infected, causing fever, malaise, lymphadenopathy, myalgia and other features closely mimicking glandular fever. Seroconversion and a broad HIV-1 specific immune response occur, usually within 30–50 days. High levels of HIV RNA are present in the blood.

HIV disease

HIV disease (symptomatic HIV infection) appears after a long incubation period which may extend over 5–15 years or more. There is a massive viraemia with wide dissemination of HIV to lymphoid organs, but the resulting immune response only partially suppresses HIV, and some virus

escapes, leading to the gradual deterioration of immune function and CD4⁺ T cells. As the CD4 count progressively declines, the person may develop:

- Infections: the most important infections are *Pneumocystis carinii* pneumonia (PCP), candidiasis (Fig. 38.1), cryptococcosis, HSV, CMV and toxoplasmosis. Tuberculosis is increasing in HIV-infected persons in whom it may involve mycobacteria resistant to a range of antitubercular drugs (multi-drug-resistant tuberculosis).
- Neoplasms: the main tumours appear to be virally related and include Kaposi sarcoma associated with HHV-8 (Fig. 38.2), lymphomas associated with EBV and cervical or anal carcinomas associated with HPV.
- Sometimes, neuropsychiatric disease: there may be dementia and other cerebral syndromes. A degenerative neurological condition characterised by a group of clinical presentations including loss of coordination, mood swings, loss of inhibitions and widespread cognitive dysfunction, is the most common central nervous system complication of HIV infection.



Figure 38.1 Candidiasis in AIDS



Figure 38.2 Kaposi sarcoma

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ryngeal candidiasis, infections of the lungs, brain, eyes and other organs, Kaposi sarcoma and lymphoma, and AIDS dementia complex.

Prognosis

The prognosis of HIV/AIDS has almost invariably been poor and death is virtually inevitable, although there are rare patients who show remarkable genetic resistance. Antiretroviral agents have been developed that can significantly slow the progression of HIV disease.

Oral features

Oral features of HIV/AIDS reflect the T-cell immune defect, and are thus mainly the consequence of fungal or viral infections (Table 38.2).

- The most common are candidiasis (candidosis) and hairy leukoplakia, but necrotising gingivitis, accelerated periodontitis, Kaposi sarcoma, lymphomas, salivary gland disease and ulcers of various aetiologies are also seen.
- These oral diseases have a number of common features, namely that generally they are:
 - not absolutely specific for HIV infection, but are more a manifestation of the immune defect; thus similar lesions can be seen in other immune defects
 - generally more likely to manifest as the CD4 cell count falls to low levels
 - some are more likely to be seen where the oral hygiene is poor
 - more likely where there is also malnutrition
 - sometimes more likely if the patient smokes tobacco
 - often controlled, at least temporarily, by antiretroviral treatment (however, some lesions – such as zoster and warts – have increased since the advent of HAART (see below)).

Diagnosis of HIV infection

Considerable compassion is called for in the diagnosis of such a catastrophic infection, since it impacts on virtually all aspects of the person's life as well as that of their family and others, eventually resulting in unpleasant, painful and incapacitating illnesses and their treatment. Confidentiality must be maintained at all times and the patient's consent and views always sought, including when considering informing other healthcare workers of any details about the person involved. There must always be appropriate counselling.

- HIV infection at the very early stage may have no detectable antibody production and thus testing the serum for HIV antibodies (serotesting)

Table 38.2 Classification of oral lesions in HIV disease**Group I** Lesions strongly associated with HIV infection

- Candidiasis:
 - erythematous
 - hyperplastic
 - thrush
- Hairy leukoplakia (EBV)
- HIV gingivitis
- Necrotising ulcerative gingivitis
- HIV periodontitis
- Kaposi sarcoma
- Non-Hodgkin's lymphoma

Group II Lesions less commonly associated with HIV infection

- Atypical ulceration (oropharyngeal)
- Idiopathic thrombocytopenic purpura
- Salivary gland diseases:
 - dry mouth
 - unilateral or bilateral swelling of major salivary glands
- Viral infections (other than EBV):
 - cytomegalovirus
 - herpes simplex virus
 - human papilloma virus (wart-like lesions) – condyloma acuminatum, focal epithelial hyperplasia and verruca vulgaris
 - varicella-zoster virus – herpes zoster and varicella

Group III Lesions possibly associated with HIV infection

- A miscellany of rare diseases

can lead to a false-negative result. Only sophisticated tests for HIV RNA will detect the virus at this stage. Eventually, usually by 6 weeks, serum antibodies to HIV become detectable.

- Acute HIV infection may well be symptomatic, but is frequently misdiagnosed unless HIV infection is considered in the differential diagnosis.
- Symptomatic HIV infection can be readily suspected by the alert clinician when the patient has obvious lesions such as *P. carinii* pneumonia (PCP), hairy leukoplakia, candidiasis or Kaposi sarcoma, particularly if more than one lesion is present or if the patient or their sexual partner is at especially high risk, such as an intravenous drug user or a promiscuous sexually active individual. CD4 lymphopenia and hypergammaglobulinaemia may suggest an immune defect, but serological confirmation of HIV infection is still required.
- The enzyme-linked immunosorbent assay (ELISA) for HIV p24 antibodies is the main serological test used, but must be repeated and may need to

be confirmed by a Western blot test. False test reactions are known, but rare.

- In many instances the clinical diagnosis is far less clear-cut, particularly in a person apparently not at obvious high risk of infection, and who has a single and otherwise common oral lesion such as an aphthous-type ulcer.

Management of HIV disease

Few, if any, patients have spontaneous remission and thus treatment is almost invariably indicated, although, in rare cases, the disease progresses very slowly and may only at a very late stage manifest with serious complications. Patient information is an important aspect in management.

Since AIDS was first recognised about 20 years ago, remarkable progress has been made in improving the quality and duration of life of HIV-infected persons. This improvement has occurred because of:

- Better recognition of opportunistic disease processes.
- Better therapy for acute and chronic complications.
- The introduction of chemoprophylaxis against PCP, toxoplasmosis, *Mycobacterium avium* complex disease, and bacterial infections. Trimethoprim-sulfamethoxazole in particular reduces not only the incidence of PCP, but also of toxoplasmosis and bacterial infections.
- The development of antiretroviral agents. However, many are liable to fairly severe adverse reactions and, perhaps more significantly, resistance has arisen (see Appendix 2).
- Protease inhibitors are used together with reverse transcriptase inhibitors as highly active antiretroviral therapy (HAART) (see p. 81).
- HAART has significantly reduced the incidence of most infections and extended life substantially. However, some infections such as herpes zoster and HPV-induced warts have increased.

There is some controversy as to at which point therapy should be introduced and as to the importance of prophylaxis of infections. Vaccines against HIV are still very much in their infancy.

Oral lesions

HIV-related oral candidiasis

Oral levels of *C. albicans* and other yeasts are increased in HIV infection, and infection is common.

Oral candidiasis is:

- the most common opportunistic infection in HIV-infected persons

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Management

Early treatment of oral candidiasis in HIV disease is warranted, not only because of the discomfort, but also because foci may act as reservoirs for spread, particularly to the oesophagus.

- Predisposing factors such as smoking and xerostomia should be controlled first.
- Antiretroviral and protease inhibitor treatment of HIV infection may aid resolution.
- Antifungals; topical therapy of candidiasis with gentian violet, nystatin, amphotericin or clotrimazole is often successful initially within about 14 days, but relapses are common and these agents are not always palatable, or accepted by children. Failures are mainly attributable to underlying immunodeficiency and poor patient compliance due to:
 - polypharmacy
 - gastrointestinal upset
 - unpalatable taste of some agents
 - drug intolerance.
- Antifungal prophylaxis should also be considered. Antifungal resistance is now a significant clinical problem in HIV-infected persons, especially in intravenous drug users, even in patients who have received no fluconazole, since resistance may be transferred and fluconazole-resistant species may be transmitted between patients. Azole resistance appears to arise because of changes in fungal enzymes or permeability. Risk factors include:
 - Severe immune defect.
 - Previous fluconazole use, especially intermittent or low-dose therapy.Fortunately, there may still be clinical response to fluconazole in fluconazole-resistant candidiasis, and amphotericin, ketoconazole and itraconazole may remain clinically effective. Therapy in fluconazole-resistant cases therefore includes: topical amphotericin or higher oral doses of fluconazole (200–600 mg/day), fluconazole suspension as an oral rinse, ketoconazole (400 mg/day) or itraconazole (200–400 mg/day).

Hairy leukoplakia

Hairy leukoplakia is a common, corrugated (or 'hairy') white lesion usually seen on the tongue mainly in HIV/AIDS and other immunocompromising states.

Hairy leukoplakia:

- may be associated with EBV
- typically affects the lateral margins of the tongue (Fig. 38.4)

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Mouth ulcers

Mouth ulcers may appear in HIV disease, but are, of course, common lesions in many non-HIV-infected persons. Ulcers may be unrelated to the HIV infection, or may be related to:

- aphthous-type ulcers, especially of the major type
- neoplasms such as Kaposi sarcoma or lymphoma
- opportunistic pathogens such as the herpesviruses (herpes simplex, varicella zoster, EBV, CMV), fungi (e.g. histoplasmosis or cryptococcosis), mycobacteria (e.g. tuberculosis or non-tuberculous mycobacteria (NTM)) or protozoa (e.g. leishmaniasis)
- drug use.

They may be part of widespread disease, such as disseminated cytomegalovirus infection, disseminated cryptococcosis or disseminated lymphoma, and thus the advice of a physician can be helpful if not mandatory. Diagnosis can be difficult and biopsy with microbial DNA studies may well be indicated. Management depends on the aetiology, but chlorhexidine and topical analgesics can be helpful. Antimicrobials or other specific therapies are often indicated to control the lesions, depending on the cause. Granulocyte colony stimulating factors or thalidomide may be helpful in aphthous-like non-specific ulceration.

Other orofacial lesions

A wide spectrum of other orofacial lesions can be seen in HIV/AIDS, including:

- Cervical lymph node enlargement, as part of persistent generalised lymphadenopathy.
- Chronic sinusitis, which may be related to bacterial or, increasingly, fungal pathogens such as aspergillosis or zygomycosis.
- Parotitis and xerostomia (HIV-salivary gland disease), seen particularly in HIV-infected children. Cystic salivary lesions are increasingly recognised.
- HPV infections, in particular genital warts (condyloma acuminata) in the mouth.
- Cranial neuropathies, such as facial palsy, pain or sensory loss.

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- release of cytokines (such as interleukin-1 and tumour necrosis factor- α)
- aggravation by trauma.

Clinical features

Mucositis presents with:

- pain
- erythema
- ulceration (Fig. 39.1)
- sometimes bleeding.

Mucositis can lead to a number of problems, including:

- significantly interfering with quality of life
- acting as a portal for septicaemia, especially streptococcal, sometimes with lethal consequences
- extending hospitalisation
- increasing costs of care.

Diagnosis

Diagnosis is clinical and it is helpful to score the degree of mucositis in order to monitor progression and therapy. The World Health Organisation toxicity grading was one of the first mucositis scales used; several others are now available (Table 39.1).



Figure 39.1 Mucositis

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- using amifostine before therapy
- betamethasone mouthwashes.

The time to healing depends on the dose intensity, but is usually complete within 3 weeks after the end of treatment. Tobacco smoking delays resolu-

Table 39.2 Management of oral complications of radiotherapy

Complication	Management
Mucositis	Prophylaxis: Amifostine 200 mg/m ² /day; Betamethasone mouthwash four times daily from the day before radiotherapy, throughout the course
osteomyelitis	Warm normal saline or benzydamine or aqueous chlorhexidine mouth baths
Xerostomia	Saliva substitute* Frequent ice cubes, popsicles or sips of water Sialogogues, e.g. pilocarpine or cevimeline
Osteoradionecrosis/irradiation-induced	Avoid by atraumatic extractions under antibiotic cover, with primary wound closure Planned pre-radiotherapy extractions or extractions within 3 months of radiotherapy
Loss of taste	Consider zinc sulphate
Trismus	Jaw-opening exercises three times daily
Ulcers	Aqueous chlorhexidine or benzydamine mouth baths four times daily
Candidiasis	Nystatin suspension 100,000 IU/ml as mouth wash four times daily Fluconazole if immunocompromised
Caries	Daily topical fluoride applications Avoid sugary diet
Dental hypersensitivity	Fluoride applications/mouthwashes
Periodontal disease	Oral hygiene Aqueous chlorhexidine mouth baths

*Artificial saliva (e.g. methylcellulose) or mucin

tion. Longer term complications of radiotherapy to the head and neck region may include:

- **Osteoradionecrosis (ORN):** potentially the most serious complication, which used to be a common complication of radiotherapy for head and neck cancers, but modern techniques have significantly reduced the risk.

The mandible, a compact bone with high density and poor vascularity, is more prone than the maxilla to ORN.

The initiating factor is often trauma, such as tooth extraction, or oral infection or ulceration from an appliance.

Factors predisposing to ORN include high radiation dose, immunodeficiency and malnutrition.

Presentation is of exposed bone in an irradiated mouth, with or without external sinuses, pain and pathological fracture.

Treatment is by long-term antibiotics, especially tetracycline (which has high bone penetrance), and local cleansing; hyperbaric oxygen may assist.

- Loss of taste.
- Cervical atherosclerosis.
- Salivary changes, which predispose to caries (Fig. 39.2), candidiasis and bacterial acute ascending sialadenitis (Fig. 39.3) (see Ch. 37) include changes that are:
 - qualitative (lowering of pH; lowering of buffering capacity; changes in electrolytes)
 - quantitative (dry mouth or xerostomia).
- Factors predisposing to salivary changes include:
 - radiation field involving major salivary glands
 - volume of salivary glands irradiated
 - salivary gland function before radiotherapy



Figure 39.2 Radiation caries

type of radiation

radiation dose

radiation fraction size and number.

- Caries rapidly progresses and affects areas usually not predisposed, such as incisal edges, smooth surfaces, and the lower incisor as well as other areas.

Chemotherapy

The oral adverse effects of chemotherapy are similar to those accompanying radiotherapy, and include:

- Mucositis, which may affect some two-thirds of patients. This is particularly severe with melphalan and etoposide.
- Infections, there is an increased liability to infections, especially candidal and herpetic. HSV is isolated from around half of oral lesions.
- Orofacial pain; related to the above and especially to chemotherapeutic agents such as vinca alkaloids and doxorubicin.
- Bleeding; there is an increased liability to gingival and oral bleeding.



Figure 39.3 Acute sialadenitis

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- bone marrow aspirate from a donor who has been stimulated with growth factors is transfused to the recipient.

This regimen results in:

- Profound immunosuppression, including a fall in salivary immunoglobulins, until the donor graft takes. Patients are thus isolated to reduce the risk of exposure to micro-organisms.
- Graft-versus-host disease (GVHD) in 60% of cases. This results from cytokine release, can produce further immune defects and is potentially lethal.
- Lymphoproliferative syndromes (post-transplant lymphoproliferative disorder (PTLD)) and lymphomas (see below) in rare patients.

Oral complications of HSCT

Oral complications are common and can be a major cause of morbidity from the effects of the underlying disease, chemo- or radiotherapy, or GVHD and include:

- Mucositis; this typically begins around 5 days post-HSCT and persists for a similar period. By around 9–14 days post-HSCT, basal cell regeneration occurs and the mucositis resolves. Apart from the measures discussed above, it may be ameliorated by use of glutamine and interleukin-11.
- Ulceration; mainly a consequence of the granulocytopenia and resolving when the neutrophil count is >500 cells/ml by around 9–14 days post-HSCT.
- Xerostomia.
- Infections.

Superficial infections are frequent and can involve a wide range of infections, mainly:

- Herpes simplex virus (HSV): about 60% of patients secrete HSV orally within 50 days, and many have lesions such as ulcers.
- Cytomegalovirus (CMV): about 60% secrete virus between days 30–150 and lesions such as ulcers may result.
- Varicella-zoster virus: 40% are infected within 6 months and 80% develop zoster.
- Epstein-Barr virus (EBV): about 60% secrete the virus and, although clinical disease is uncommon, hairy leukoplakia or lymphoproliferative disease may result.
- Human papilloma viruses (HPV): can cause extensive lesions over the 3–8 months post-transplant.
- Candidiasis: carriage and oral lesions are almost invariable in the absence of prophylactic antifungal therapy.

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- hairy leukoplakia
- sclerodermatous syndrome
- ciclosporin may induce gingival swelling.

Diagnosis of GVHD is from the history and clinical features and a mucosal or labial salivary gland biopsy which show mononuclear cell infiltrates.

Management of GVHD oral lesions is best with use of:

- oral hygiene measures
- analgesics (morphine or hydromorphone)
- topical azathioprine or ciclosporin
- non-alcoholic chlorhexidine mouth rinses
- nystatin mouth washes (5,000,000 units) or fluconazole
- pilocarpine
- xylitol chewing gum
- artificial saliva
- growth factors.

Solid organ transplantation

Immunosuppressive therapy is universally used after transplantation, with the potential problems outlined below.

Immunosuppression

Immunosuppressive therapy with corticosteroids, azathioprine or other agents is used especially to:

- Suppress rejection in transplant recipients (bone marrow, kidney, liver, pancreas, heart and heart-lung); these are the most severely immunocompromised patients.
- Treat autoimmune disorders.
- Treat connective tissue diseases.
- Control some malignant tumours, especially lymphoproliferative neoplasms.

A variety of drugs are used for immunosuppression, especially corticosteroids, ciclosporin, tacrolimus and sirolimus. Drugs which are cytotoxic to a range of cells, including some immunocytes, such as azathioprine, cyclophosphamide and chlorambucil are also used as immunosuppressives.

Patients on immunosuppressive agents are at risk from oral infections, which may be opportunistic (involving micro-organisms that are normally commensal) or may involve exogenous pathogens. Infections include:

- Fungal infections:

Candidiasis (see Ch. 21).

Aspergillus spp. may infect the paranasal sinuses, palate or other sites by direct extension and haematogenously. Diagnosis is by demonstration of hyphae in a smear, serology and biopsy. Intravenous amphotericin may be effective.

Mucormycosis (zygomycosis: phycomycosis) is infection by *Mucor* or *Rhizopus* spp., mainly of the paranasal sinuses and nose of immunosuppressed or poorly controlled diabetic or leukaemic patients.

Diagnosis is by biopsy and culture; treatment is by control of underlying disease, debridement and intravenous amphotericin.

- Mycobacterioses.
- Herpetic infections; aciclovir by slow intravenous infusion or orally, repeated 8-hourly, is indicated for severe herpes virus infections in immunocompromised patients
- Odontogenic infections are potentially life-threatening in the immunosuppressed patient, and broad-spectrum cover is needed (such as penicillin plus gentamicin).

Patients may also be at risk from attempts at treatment; thus for example, broad-spectrum antibiotics used to control bacterial infections increase the hazard of fungal infections. Neoplasms may also be a risk in chronic immunosuppression, at least some of which are virally related, including:

- Kaposi sarcoma.
- Lymphoproliferative syndromes (PTLD), which may appear late – even many years after transplantation – and range from hyperplastic-appearing lesions to non-Hodgkin's lymphoma or multiple myeloma. Reduction in immunosuppressives can reverse PTLD. Surgical resection, cytotoxics, anti-CD21 and anti-CD24 antibodies, interferon- α and rituximab have been effectively used for treatment.
- Squamous cell carcinomas of the skin and of the lip.

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Appendices

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Appendix 1

PDFFREE COMUNIDAD ODONTOLOGICA

Oral Manifestations of Disorders of Specific Systems

This appendix annotates the orofacial manifestations of disorders of specific systems: further details can be found elsewhere in this book.

Table A1.1 Cardiovascular disease

Angina pectoris

- Pain referred to jaw rarely

Anticoagulants

- Bleeding tendency

Giant cell arteritis (cranial or temporal arteritis)

- Pain usually over the temple
- Rarely, tongue pain or ischaemic necrosis

Hereditary haemorrhagic telangiectasia

- Telangiectasias that may bleed profusely

Hypertension (problems caused by some antihypertensive agents)

- Dry mouth
- Gingival swelling (nifedipine)
- Lichenoid lesions (methyldopa, ACE inhibitors)

Polyarteritis nodosa

- Ulcers

Shunts: right to left (e.g. Fallot's tetralogy)

- Cyanosis
- Delayed tooth eruption

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Table A1.7 Contd

Mumps

- Salivary gland swelling

Papilloma viruses

- Warts
- Papillomas
- Condyloma acuminata
- Focal epithelial hyperplasia

Paracoccidioidomycosis

- Ulcers

Rubella

- Palatal petechiae
- Dental hypoplasia in congenital rubella

Syphilis

- Chancre

Syphilis – Contd

- Mucous patches
- Ulcers
- Gumma
- Pain from neurosyphilis
- Leukoplakia
- Lymph node enlargement
- Hutchinson's teeth in congenital syphilis

Toxoplasmosis

- Cervical lymph node enlargement

Tuberculosis (including atypical mycobacteria)

- Ulcers rarely
- Cervical lymph node
- Enlargement

Table A1.8 Liver disorders

Alcoholic cirrhosis

- Bleeding tendency
- Sialosis

Biliary atresia

- Dental hypoplasia
- Pigmented teeth

Chronic active hepatitis

- Lichen planus

Hepatitis C

- Salivary swelling and xerostomia
- Lichen planus

Jaundice

- Bleeding tendency
- Jaundice

Kernicterus

- Dental hypoplasia
- Pigmented teeth

Primary biliary cirrhosis

- Sjögren syndrome
- Lichen planus

Table A1.9 Metabolic disorders

Amyloidosis

- Macroglossia
- Purpura

Erythropoietic porphyria

- Reddish teeth
- Bullae/erosions
- Dental hypoplasia

Folic acid deficiency

- Burning mouth syndrome
- Ulcers
- Glossitis
- Angular cheilitis

Hypophosphataemia

- Dental hypoplasia
- Large pulp chambers

Hypophosphatasia

- Loosening and loss of teeth (hypoplastic cementum)

Iron deficiency

- Burning mouth syndrome
- Ulcers
- Glossitis
- Angular cheilitis

Lesch–Nyhan syndrome (congenital hyperuricaemia)

- Self-mutilation

Mucopolysaccharidosis

- Spaced teeth
- Retarded tooth eruption
- Temporomandibular joint anomalies
- Enamel defects
- Cystic lesions

Neimann–Pick disease

- Retarded tooth eruption
- Loosening of teeth
- Mucosal pigmentation

Rickets (vitamin D dependent)

- Dental hypoplasia
- Large pulp chambers

Scurvy

- Gingival swelling
- Purpura
- Ulcers

Tangier disease

- Orange tonsillar deposits

Vitamin B₁₂ deficiency

- Burning mouth syndrome
- Ulcers
- Glossitis
- Angular cheilitis

Table A1.10 Neurological disorders**Bulbar palsy**

- Fasciculation of tongue

Cerebral palsy

- Spastic tongue
- Dysarthria
- Attrition

Cerebrovascular disease

- Facial palsy

Choreoathetosis

- Green staining of teeth in kernicterus

Disseminated sclerosis

- Pain
- Sensory loss
- Facial palsy

Down syndrome

- Delayed tooth eruption
- Macroglossia
- Scrotal tongue
- Maxillary hypoplasia
- Anterior open bite
- Hypodontia
- Periodontal disease
- Cheilitis

Epilepsy

- Trauma to teeth/jaws/mucosa
- Gingival swelling if on phenytoin

Facial palsy

- Palsy and poor natural cleansing of mouth on same side

Neurosyphilis

- Pain rarely
- Dysarthria
- Tremor of tongue

Parkinsonism

- Drooling
- Tremor of tongue

Riley-Day syndrome

- Self-mutilation
- Prominent fungiform papillae
- Salivary swelling
- Sialorrhoea

Trigeminal neuralgia

- Pain

Table A1.11 Psychiatric disorders**Anxiety states**

- Dry mouth
- Cheek biting
- Bruxism

Bulimia

- Tooth erosion

Depression, hypochondriasis and various psychoses

- Dry mouth
- Discharges
- Pain

Depression, hypochondriasis and various psychoses – Contd

- Disturbed taste
- Disturbed sensation
- Artefactual ulcers

Drug abuse

- Oral burns
- Bruxism

Munchausen syndrome

- Self-mutilation
- Feigned dental disease

Table A1.12 Renal disorders**Chronic renal failure**

- Xerostomia
- Halitosis/taste disturbance
- Leukoplakia
- Dental hypoplasia in children
- Renal osteodystrophy
- Bleeding tendency

Nephrotic syndrome

- Dental hypoplasia

Post-renal transplantation

- Infections, particularly herpetic and candidal
- Bleeding tendency
- Gingival swelling if on ciclosporin or nifedipine

Renal rickets (vitamin D resistant)

- Delayed tooth eruption
- Dental hypoplasia
- Enlarged pulp

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Table A1.14 Skin diseases

Chronic bullous disease of childhood

- Ulcers
- Blisters, rarely
- Desquamative gingivitis

Darier's disease

- White lesions

Dermatitis herpetiformis

- Ulcers
- Blisters, rarely
- Desquamative gingivitis

Ectodermal dysplasia

- Hypodontia
- Dental anomalies (peg-shaped teeth)

Ellis-van Creveld syndrome (chondroectodermal dysplasia)

- Multiple fraeni
- Short roots
- Hypodontia

Epidermolysis bullosa

- Blisters
- Erosions
- Scarring
- Dental hypoplasia

Erythema multiforme

- Ulcers
- Blood-stained crusting of lips

Lichen planus

- White lesions
- Red lesions
- Erosions
- Desquamative gingivitis

Linear IgA disease

- Ulcers
- Blisters, rarely
- Desquamative gingivitis

Pemphigoid

- Blisters
- Ulcers
- Desquamative gingivitis

Pemphigus

- Ulcers
- Blisters, rarely
- Desquamative gingivitis

Psoriasis

- White lesions
- Lesions like erythema migrans

Toxic epidermal necrolysis

- Ulcers

Appendix 2

PDFFREE COMUNIDAD ODONTOLOGICA

Agents used in the Treatment of Patients with Oral Disease

Table A2.1 Agents which may reduce pain from mucosal lesions

Agent	Use
Benzydamine hydrochloride	Rinse or spray every 1.5–3 hours
Lidocaine	Topical solution may ease pain
Carboxymethylcellulose	Paste or powder used after meals to protect area

Table A2.2 Various toothpastes

Characteristic	Main UK trade name
Normal fluoride	Macleans Freshmint/Coolmint*
High fluoride	Colgate Triple Cool Stripe* Colgate Ultra Cavity Protection* Crest Complete*
Low fluoride	Macleans Milk teeth* Macleans Milk teeth gel*
Against sensitivity	Macleans Sensitive*
Against gingival disease/caries/tartar	Colgate Total* Crest Complete*
Whitening	Macleans Whitening Toothpaste*
No additives	Kingfisher

*Toothpastes accredited by the British Dentistry Association

Table A2.3 Some mouthwashes with antimicrobial activity

Agent	Dose	Comments*
Chlorhexidine gluconate	0.12–0.2% aqueous mouthwash, rinse for 1 minute twice daily. Also 0.5–1.0% gel or spray	A cationic chlorinated bisbiguanide with significant antiplaque and antifungal activity and oral retention; traces can still be found in saliva after 24 hours. May stain teeth if patient drinks tea, coffee or red wine
Triclosan	0.03% mouthwash, rinse for 1 minute twice daily	A non-ionic chlorinated bisphenolic antiseptic with moderate antiplaque and antifungal activity, but less retention in mouth than chlorhexidine. More effective against plaque when with copolymer or zinc citrate
Cetylpyridinium chloride	0.05% mouthwash used twice daily	A quaternary ammonium compound with antiplaque activity, but less than chlorhexidine. May stain teeth and cause oral burning sensation or ulceration

*All occasionally may cause mucosal irritation

Table A2.4 Some analgesics

Agent	Adult dosage	Contraindications
Non-steroidal anti-inflammatory drugs (NSAIDs)		
Ibuprofen	400 mg up to 4 times daily	Asthma, peptic ulcer, bleeding tendency, breast-feeding, cardiac renal and liver disease, pregnancy, elderly, aspirin hypersensitivity
Mefenamic acid	250–500 mg up to 3 times daily	Asthma, peptic ulcer, bleeding tendency, breast-feeding, cardiac renal and liver disease, pregnancy, elderly, aspirin hypersensitivity
Celecoxib (Cox-2 inhibitor)	100 mg twice daily	Asthma, peptic ulcer, bleeding tendency, breast-feeding, cardiac renal and liver disease, pregnancy, elderly, aspirin hypersensitivity
Non-NSAIDs		
Paracetamol (acetaminophen)	500–1000 mg up to 6 times daily (max. 4 mg/day)	Liver or renal disease; those on zidovudine
Nefopam	30–60 mg up to 3 times daily	Convulsive disorders, pregnancy, elderly, renal, liver disease
Opioids		
Codeine phosphate	10–60 mg up to 6 times daily orally (or 30 mg i.m.)	Liver disease, late pregnancy
Dihydrocodeine	30 mg up to 4 times daily (or 50 mg i.m.)	Children, hypothyroidism, asthma, renal disease
Pentazocine	25–50 mg up to 4 times daily (or 30 mg i.m. or i.v.)	Pregnancy, children, hypertension, respiratory depression, head injuries or raised intracranial pressure
Dextromoramide	5 and 10 mg tablets	Patients with head injury (since it interferes with pupillary responses and suppresses respiration), liver disease, kidney disease, pregnancy, breast-feeding, taking monoamine oxidase inhibitors
Methadone	5 mg tablets	The elderly or debilitated patient, as accumulation occurs

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Table A2.6 Suggested topical corticosteroid creams

Medium potency	High potency	Super potency
0.1% Triamcinolone acetonide; Adcortyl cream	0.5% fluocinonide; Metosyn cream	0.5% clobetasol propionate; Dermovate cream
0.025% fluocinolone acetonide; Synalar cream or gel	0.25% desoximetasone; Stiedex cream	0.05% betamethasone dipropionate; Diprosone cream
0.05% betamethasone valerate; Betnovate cream	0.1% halcinonide; Halciderm topical cream	0.05% halobetasol propionate-
0.05% fluticasone propionate; Cutivate cream	-	-

Table A2.7 Alternative topical immunosuppressants

Drug	Dose	Comments
Ciclosporin (Neoral or Sandimmun), used as mouthwashes or in an adhesive medium Orabase-like preparation	100-1500 mg/ml daily as a mouthwash; <50 mg/ml daily in an adhesive preparation	Adverse effects rare with topical applications
Tacrolimus (Protopic or Prograf)	0.1-0.03% ointment	Adverse effects rare with topical applications. Has 10- to 100-fold potency of ciclosporin

Table A2.8 Systemic immunosuppressants and immunomodulatory agents

Drug	Dose	Comments*
Azathioprine	2–2.5 mg/kg daily (50–150 mg/day)	May take 2–3 months to have real effect. May cause bone marrow suppression, so thiopurine methyl transferase (TPMT) levels should first be assayed to detect genetic polymorphisms at risk (1:300). May also cause liver dysfunction, arrhythmias, hypotension, nephritis. Contraindicated in pregnancy. Small risk of cancer with prolonged use. Interactions: allopurinol (increases the effect of azathioprine), acetylsalicylic acid (bleeding), other immunosuppressants (increase the risk of infection)
Ciclosporin (cyclosporin)	1–2 mg/kg daily	Nephrotoxic, hepatotoxic. May cause hypertension, blood dyscrasias, gingival swelling. Contraindicated in kidney disease, pregnancy, porphyria. Interactions: allopurinol, analgesics and antifungals (increase ciclosporin toxicity), anti-epileptic drugs (reduced efficiency)
Colchicine	500 µm 3 times daily	May cause diarrhoea and bone marrow suppression. Contraindicated in pregnancy, elderly, cardiac, renal or hepatic disease
Cyclophosphamide	1–2 mg/kg daily	Can cause bone marrow suppression, cystitis. Small risk of cancer with prolonged use
Dapsone	1 mg/kg daily (usually 100–200 mg). Give also vitamin E 800 IU/day	Contraindicated in G6PD daily deficiency (test for this before starting treatment and then monitor reticulocyte count closely), pregnancy, cardiorespiratory disease. Can cause haemolysis and methaemoglobinaemia. Can interfere with liver and blood platelet function. Main adverse effects: anaemia, rashes, neuropathy, headache, liver toxicity. Interactions: trimethoprin and methotrexate (increase the risk of haematological complications)

Contd

Table A2.8 Contd

Drug	Dose	Comments*
Hydroxychloroquine	200–400 mg/day	May take 3–6 months to have effect. May cause retinal damage and visual impairment. May cause bone marrow suppression. Contraindicated in patients with renal or hepatic disease
Levamisole	50 mg 3 times daily for 3 days	Promotes leucocyte chemotaxis. May cause dizziness, taste disturbance, nausea, agranulocytosis
Mycophenolate	1 g twice daily	May take 2–3 months to have real effect. Used in transplants mainly. May cause bone marrow suppression. Contraindicated in pregnancy
Pentoxifylline	400 mg twice daily	Contraindicated in cerebrovascular haemorrhage, myocardial infarction
Prednisolone (give as enteric coated prednisolone with meals)	Initially 30–80 mg orally each day in divided doses, reducing as soon as possible to 10 mg/day	May produce adrenal suppression. Limit dosage in hypertension and diabetes mellitus. May cause weight gain, osteoporosis
Tacrolimus	100 µm/kg daily	Used in transplants mainly. May cause cardiomyopathy. Contraindicated in pregnancy
Thalidomide	50–200 mg/day at night initially, then alternate-day therapy	Anti-tumour necrosis factor. May take 2–3 months to have real effect. Causes drowsiness in up to 50%. Teratogenic. Neurotoxic; may cause axonal neuropathy, so take sensory nerve action potential (SNAP) records in sural and median nerves every 6 months. This is dose-related, and in 50% is irreversible: most neuropathy has occurred in patients taking 100 mg/day or more for 6 months or longer. Other effects include constipation, rash, oedema and reversible lymphopenia

*Many can increase liability to infection and, long-term, possibly also neoplasia

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Table A2.10 Antifungals

Agent	Dosage and duration (continue for at least 48 h after lesions have cleared)*	Possible drug interactions and contraindications [†]
Chlorhexidine	0.12–0.2% mouth rinse twice daily	Tooth staining, especially if the patient drinks tea, coffee or red wine
Amphotericin	10 mg lozenge, 100 mg/ml suspension, 10–400 mg 6 hourly for at least 14–21 days	Topical use; no problems
Amphotericin (i.v.)	0.5 mg/kg for at least 10–14 days	Expensive. Nephrotoxicity, arrhythmias, neuropathies, anaphylactoid reactions. Avoid in pregnancy. Liposomal amphotericin may be safer
Nystatin (topical)	500,000 IU lozenge, 100,000 IU pastille, 100,000 IU per ml of suspension. 100,000 IU 6 hourly for at least 14–21 days. Suspension contains sucrose	Topical use; often no problems, but may be unpleasant taste, nausea or gastrointestinal disturbance
Clotrimazole (topical)	10 mg 6 hourly for at least 14 days. Contains sucrose. Not available in the UK	Difficult to dissolve if mouth dry
Miconazole (topical)	250 mg tablet, 25 mg/ml gel. 250 mg 6 hourly for at least 14–21 days 50 mg/g denture lacquer; apply weekly for at least 2 weeks. Not available in the USA	May interact with many drugs, including antidiabetic drugs, anticoagulants, phenytoin, midazolam, ciclosporin Cisapride and terfenadine. Avoid in pregnancy, porphyria. May impair oral contraceptive. Even topical agent may be absorbed systemically
Ketoconazole (oral)	200–400 mg/day for at least 14 days	Not absorbed in achlorhydria. May interact with many drugs, including anticoagulants, phenytoin, midazolam, ciclosporin, sertindole, terfenadine, cisapride, cimetidine and ranitidine

Contd

Table A2.10 Contd

Agent	Dosage and duration (continue for at least 48 h after lesions have cleared)*	Possible drug interactions and contraindications†
		(reduced absorption), isoniazid and rifampicin (reduce the effect of this drug), antidiabetic drugs (increase the effect of this drug). Enhances nephrotoxicity of ciclosporin. Avoid in pregnancy, porphyria. Hepatotoxic. Expensive. May impair oral contraceptive
Fluconazole (oral)	50–200 mg/day for at least 14 days	May interact with many drugs, including antidiabetic drugs, anticoagulants, phenytoin, midazolam, ciclosporin, zidovudine, terfenadine, cisapride. Avoid in pregnancy, porphyria. May sometimes be hepatotoxic and myelosuppressive. Expensive. May impair oral contraceptive. Avoid in pregnancy, infants, renal disease. Less toxic than ketoconazole
Itraconazole (oral)	100–200 mg/day for at least 14 days. 10 mg/ml liquid 10 ml twice daily for at least 14 days	Not absorbed in achlorhydria. May interact with many drugs, including digoxin, sertindole, anticoagulants, phenytoin, midazolam, ciclosporin, simvastatin, terfenadine, cisapride. Avoid in cardiac disease, pregnancy, porphyria. Expensive. May impair oral contraceptive

*The higher doses are used in HIV infection

†Check pharmacopoeia for other contraindications, cautions and interactions

Table A2.11 Nucleoside reverse transcriptase inhibitors (NRTIs)

Proper name	Trade name	Possible orofacial adverse effects	Other main adverse effects
Zidovudine (azidothymidine) AZT ZDV	Retrovir	Erythema multiforme, hyperpigmentation	Nausea, diarrhoea, bone marrow suppression, lactic acidosis, myopathy
Didanosine DDI	Videx	Erythema multiforme, xerostomia	Nausea, diarrhoea, lactic acidosis, pancreatitis, abnormal liver function, peripheral neuropathy, retinal damage
Zalcitabine DDC	Hivid	Erythema multiforme, ulcers	Lactic acidosis, pancreatitis, nausea, diarrhoea, abnormal liver function
Abacavir ABC	Ziagen	Erythema multiforme	Lactic acidosis, nausea, diarrhoea, life-threatening rash
Lamivudine 3TC	Epivir	Xerostomia	Nausea, diarrhoea, pancreatitis, abnormal liver function
Stavudine D4T	Zerit	–	Neuropsychiatric reactions, abnormal liver function

Table A2.12 Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Proper name	Trade name	Possible orofacial adverse effects	Other main adverse effects
Nevirapine	Viramune	Erythema multiforme, ulcers	Induces liver drug-metabolising enzymes, abnormal liver function
Efavirenz	Sustiva	Erythema multiforme	Interferes with liver drug-metabolising enzymes, neuropsychiatric reactions
Delavirdine	Rescriptor. Not licensed in the UK	Erythema multiforme	Inhibits liver drug-metabolising enzymes

Table A2.13 Protease inhibitors

Proper name	Trade name	Possible orofacial adverse effects	Other main adverse effects
Indinavir IDV	Crixivan	Cheilitis, parotid lipomatosis, xerostomia, taste disturbance	Interferes with liver drug-metabolising enzymes, nephrolithiasis, oesophagitis, haemolysis, dyslipidaemia
Nelfinavir NFV	Viracept	Parotid lipomatosis, xerostomia	Nausea, diarrhoea, interferes with liver drug-metabolising enzymes, dyslipidaemia
Amprenavir APV	Agenerase. Not licensed in the UK	Perioral paraesthesia, parotid lipomatosis	Interferes with liver drug-metabolising enzymes, dyslipidaemia
Ritonavir RTV	Norvir	Perioral paraesthesia, parotid lipomatosis, xerostomia, taste disturbance, facial oedema	Nausea, diarrhoea, interferes with liver drug-metabolising enzymes, flushing, dyslipidaemia
Saquinavir SQV	Fortovase, Invirase	Erythema multiforme, ulcers, parotid lipomatosis, xerostomia	Nausea, diarrhoea, interferes with liver drug-metabolising enzymes, dyslipidaemia

Table A2.14 Anxiolytics

Drug	Dose	Comments
Diazepam	2–30 mg/day in divided doses	Avoid in glaucoma. Use with caution in the elderly
Temazepam	5–10 mg at night	Avoid in glaucoma. Use with caution in the elderly

Table A2.15 Some antidepressants

Drug	Dose	Comment
Amitriptyline	25–75 mg/day in divided doses	Contraindications: recent myocardial infarction, arrhythmias, liver disease
Clomipramine	25 mg 3 times daily or 75 mg at night	Contraindications: recent myocardial infarction, arrhythmias, liver disease
Dothiepin (dosulepine)	25 mg 3 times daily or 75 mg at night	Contraindications: recent myocardial infarction, arrhythmias, liver disease
Doxepine	10–100 mg/day in divided doses	Contraindications: recent myocardial infarction, arrhythmias, liver disease
Fluoxetine	20 mg/day	Caution with: epilepsy; pregnancy; cardiac, liver or kidney disease; allergy; mania
Venlafaxine	75 mg in morning	Contraindications: recent myocardial infarction, arrhythmias, liver disease

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ISBN 0-7236-1074-6



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